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THE UNIVERSITY OF ALBERTA

THE SYNTHESIS OF SOME 3-INDOLYL THIOETHERS

by

ROY VERNON JARDINE, B.A.

A THESIS

Submitted to the Faculty of Graduate Studies in  
partial fulfilment of the requirements for the  
degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA  
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1964





UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read,  
and recommend to the Faculty of Graduate  
Studies for acceptance, a thesis entitled:

"THE SYNTHESIS OF SOME 3-INDOLYL THIOETHERS"

submitted by ROY VERNON JARDINE

in partial fulfilment of the requirements  
for the degree of Doctor of Philosophy.





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## ABSTRACT

Several possible synthetic sequences leading to the formation of 3-alkylthioindoles have been investigated.

The Williamson ether synthesis involving reactions between either 3-haloindoles and salts of mercaptans in dimethylformamide, or indolyl mercaptide and aralkyl halides in tetrahydrofuran were generally unsuccessful. This was attributed, in the case of the haloindoles, to the unstable nature of the haloindole involved. Separate experiments showed for example, that under the general conditions employed, 3-bromoindole was almost quantitatively converted into indole. However, there was evidence that some 3-alkylthioindole had been formed but this could not be isolated from the mixture. In the second case, preferential reaction on the nitrogen atom, rather than on the sulphur atom of 3-indolyl mercaptides by benzyl iodide thwarted attempts to secure the expected thioindole.

Although thioethers have been prepared by the reaction of Grignard reagents with sulfenyl halides, the reaction between indolyl magnesium bromide and ethyl sulfenyl chloride, proved to be very complex, affording a mixture containing not only the expected indolyl thioether, but also significant amounts of diindolyl sulphide and 3-ethylindole. Isolation of the 3-ethylthioindole by distillation methods proved to be impractical due to much decomposition. Although G.L.C. appeared to effectively separate the products of the reaction this method also was impractical. Several experiments which aimed at the elucidation



of the route by which these transformations occurred failed to provide satisfaction.

Two routes to alkyl 3-indolyl thioethers were found to be useful. The first of these employed the well known Fischer indole synthesis to the cyclization of the phenylhydrazone of ethylthioacetaldehyde using boron trifluoride as catalyst. Difficulties encountered in the preparation of the required acetals from which the phenylhydrazones could be made, limited somewhat, the general applicability of this method.

The second, and apparently more general method involved the synthesis and subsequent reduction of 1,2-dithiolo[4,3-b]indole-3(4H)-thione, followed by treatment with a suitably activated organic halide. The resulting indole dithiocarboxy esters could be hydrolysed readily to substituted 3-alkylthio-2-indole carboxylic acids, which were easily decarboxylated to afford the required 3-alkylthioindoles.

Finally, a spectrophotometric\* method to determine the position of substitution of the pyrrole ring of the indole nucleus has been developed. It was shown that position of the signal for the C<sub>2</sub> proton in indole or 3-substituted indoles was strongly dependent upon the solvent employed for the spectral determination. On the other hand, the signal position for the C<sub>3</sub> proton was much less affected by the nature of the solvent used. The utility of this solvent effect on the chemical shift to distinguish between 2 and 3 substitution of the indole nucleus has been pointed out.

\* Nuclear Magnetic Resonance Spectrometry.





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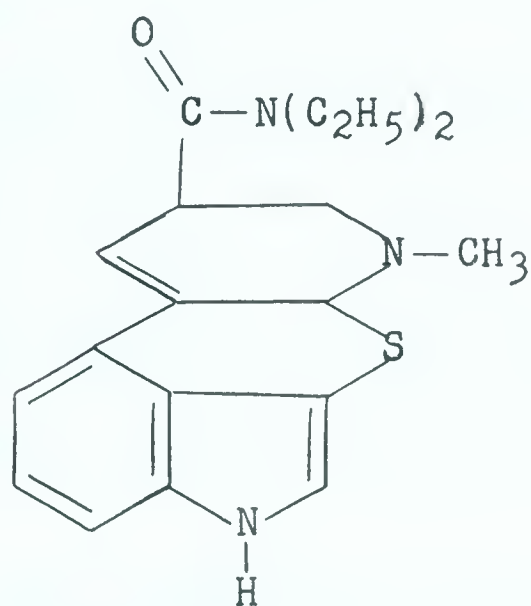
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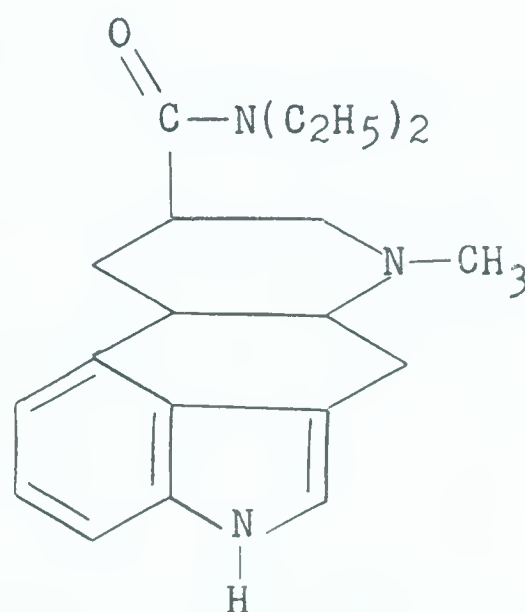
## INTRODUCTION

### 1. The Problem.

The main theme of this thesis is the synthetic means by which a sulphur atom can be introduced into the 3-position of the indole nucleus thus leading to the formation of 3-indolyl thioethers. This is the primary phase in the ultimate aim of discovering a route for the preparation of the sulphur analogue of lysergic acid diethyl amide (I).



I



II

A number of cases are known where replacement of a methylene group by a sulphur moiety in a physiologically active compound produces a structure which retains its activity in modified form. For example, 2-acetylaminofluorene and its sulphur analogue, 3-acetylaminodibenzothiophene are both potent carcinogens (1).

The interesting physiological properties of d-lysergic acid diethylamide (II), first described by Hofmann (2,3) resulted in consideration of the corresponding sulphur analogue of lysergic





acid diethylamide (I) as a potential psychotomemetic\* substance.

In addition it was felt necessary to seek a simple spectrophotometric method to determine whether substitution had occurred at position 2 or 3 in the indole nucleus.

Pertinent also to this problem was a study of the peculiar reactions and properties of 3-bromoindole which was involved in one proposed route to the 3-mercaptoindole derivatives.

## 2. Literature Survey.

In the preparation of 3-indolyl thioethers two features require consideration. One is the formation of the carbon-sulphur bond either before or after formation of the indole ring system, the other, the introduction of substituents into the specific position of indole. A brief outline of the available methods by which these goals may be achieved might be of help in understanding the present problem.

### A. General Methods for the Preparation of Unsymmetrical Thioethers.

#### (a) Thioethers from Alkyl (Aryl) Halides.

By formal analogy to the Williamson ether synthesis, thioethers may be prepared by the reaction of the salt of a mercaptan with an alkyl or aryl halide. The utility of this reaction lies in the fact that it may proceed by two different routes,

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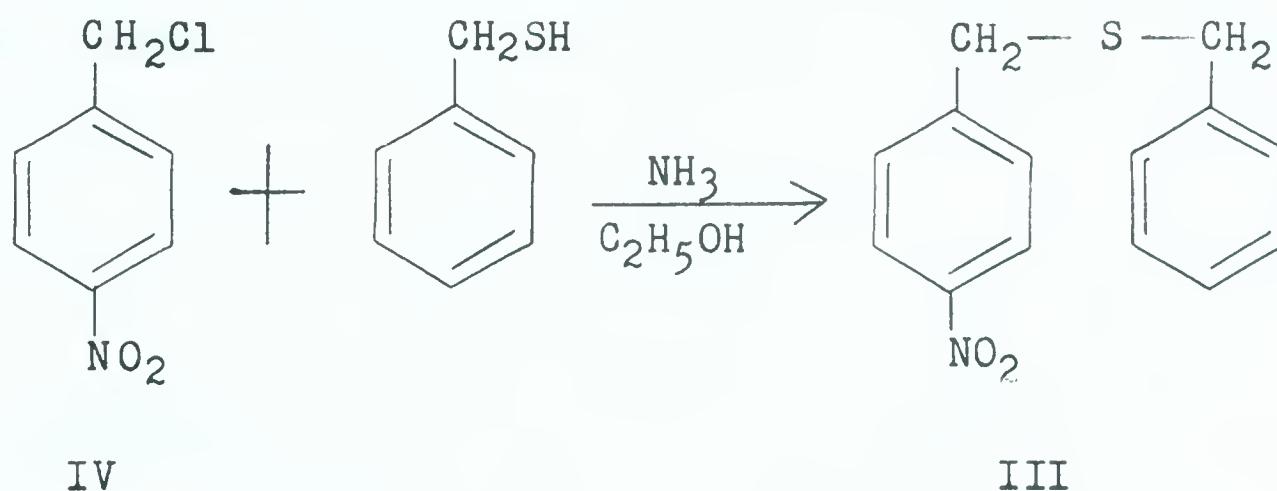
\* As defined by D. F. Downing (4).



to yield the same thioether, as the following generalized examples indicate.



The reaction may be exemplified by the preparation of 4-nitrodibenzyl sulphide (III) from p-nitrobenzyl chloride (IV) in 95% yield (5).

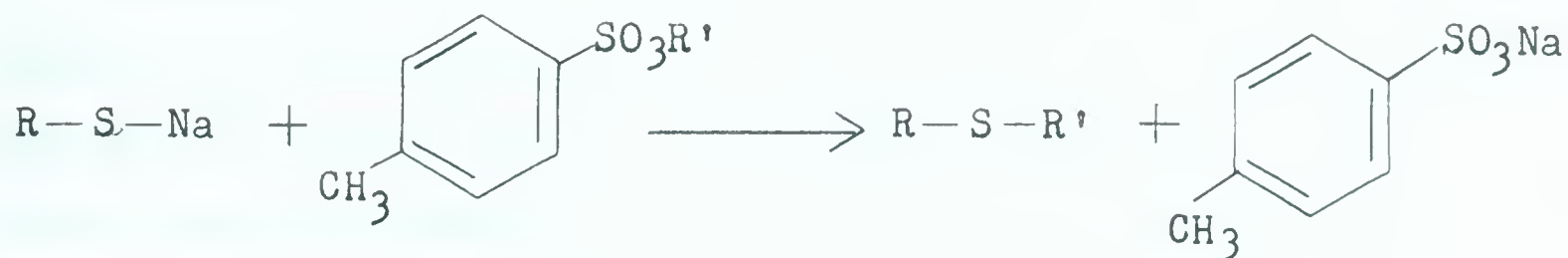


An extension of this procedure is the reaction of salts of mercaptans with esters of sulphuric or sulphonic acids. By this



method n-dodecyl p-tolyl sulphide has been prepared from p-thio-cresol and n-dodecyl p-toluenesulphonate, in 83.2% yield (6).

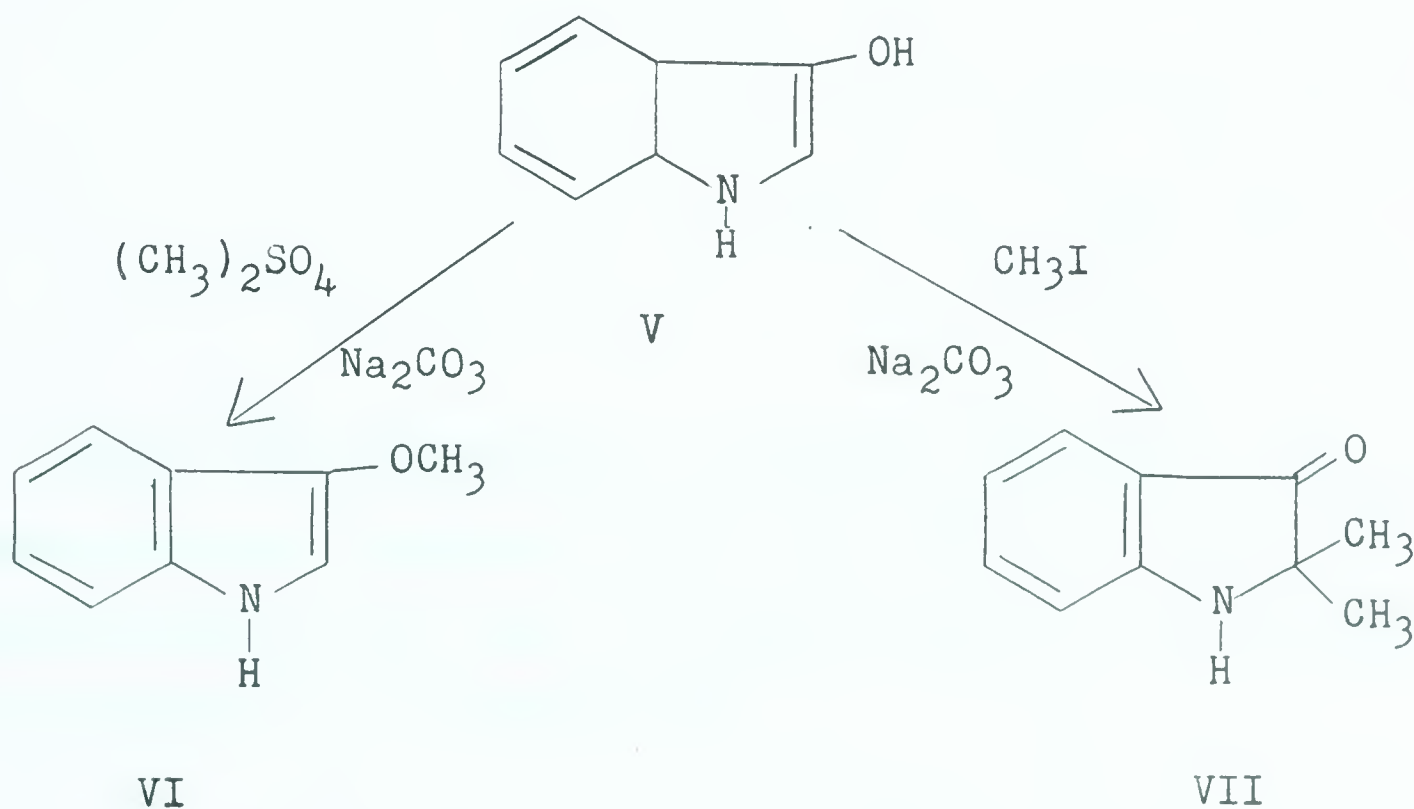




R = p-tolyl

R' = n-dodecyl

It is of interest to note that 3-hydroxyindoles give two different products when subjected to reactions with alkylating agents, depending upon reaction conditions. Thus methylation of indoxyl (3-hydroxyindole) (V) with methyl sulphate in the presence of base affords 3-methoxyindole (VI), whereas treatment



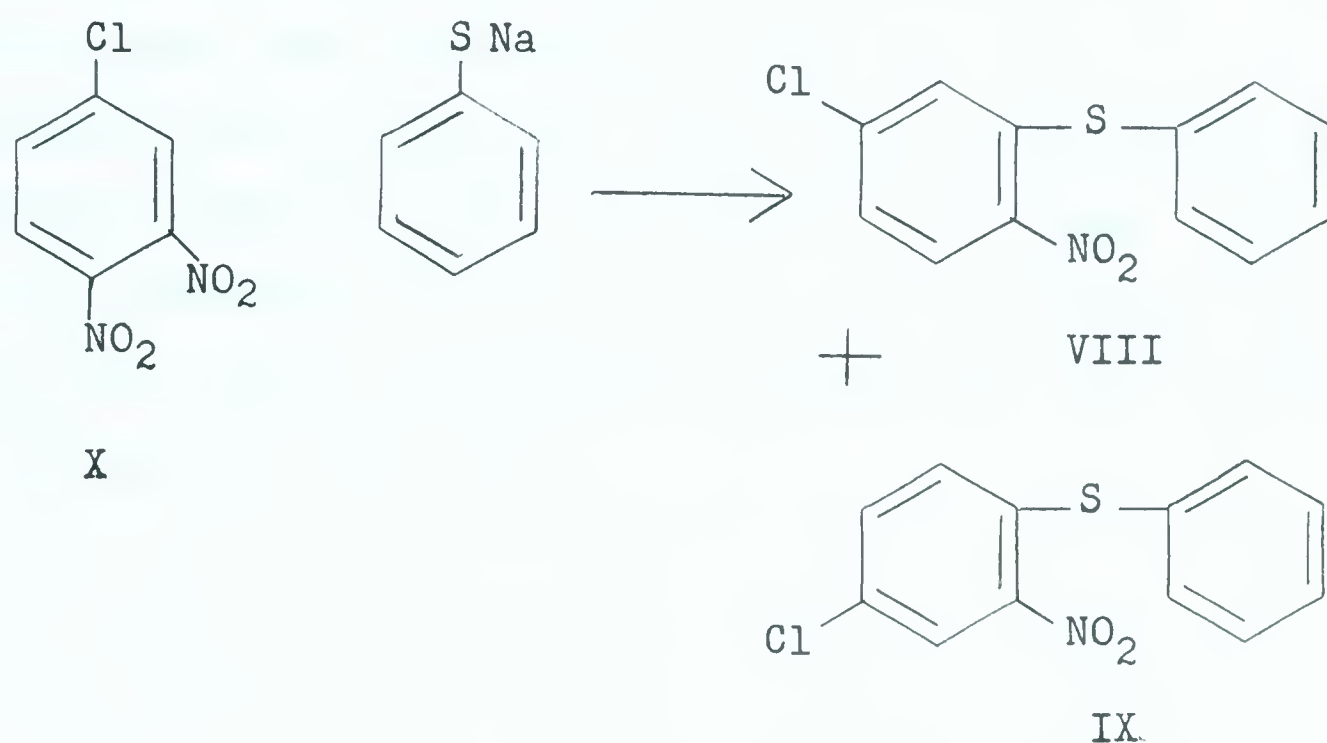
with methyl iodide results in C-methylation, with the formation of 2,2-dimethylindoxyl (VII) (7).



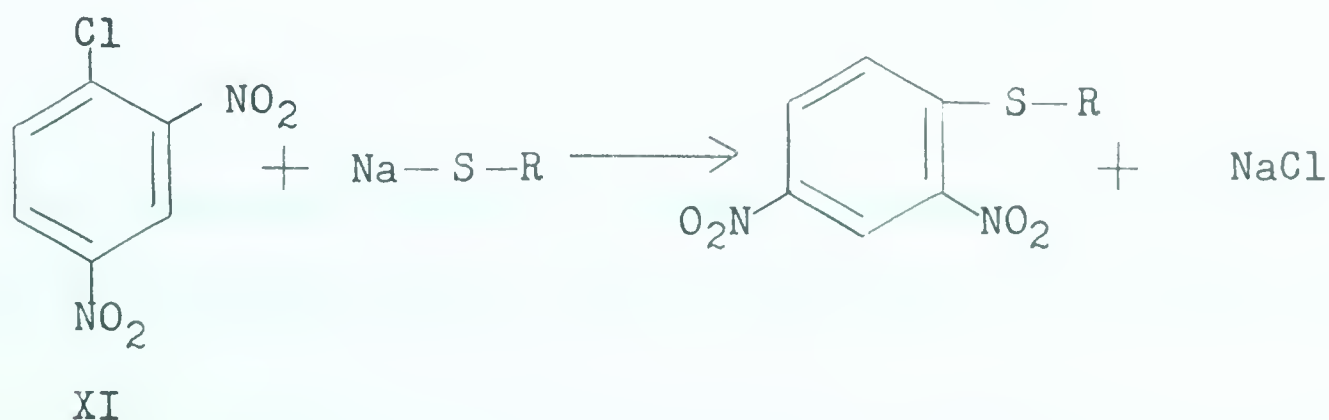


(b) Thioethers from Mercaptans and Nitro Compounds

Analogous to a displacement carried out on an alkyl (aryl) halide, is the replacement of a nitro group in a sufficiently activated aromatic nucleus by an aryl mercaptide. Thus 5-chloro-2-nitrodiphenyl sulphide (VIII), along with a small quantity of 4-chloro-2-nitrodiphenyl sulphide (IX), is produced when 1-chloro-3,4-dinitrobenzene (X) is treated with sodium phenyl mercaptide (8).



These displacements are in distinct contrast to the reaction with mercaptans exhibited by the more familiar isomer, 2,4-dinitrochlorobenzene (XI), a classic reagent for the preparation of derivatives of mercaptans (9).

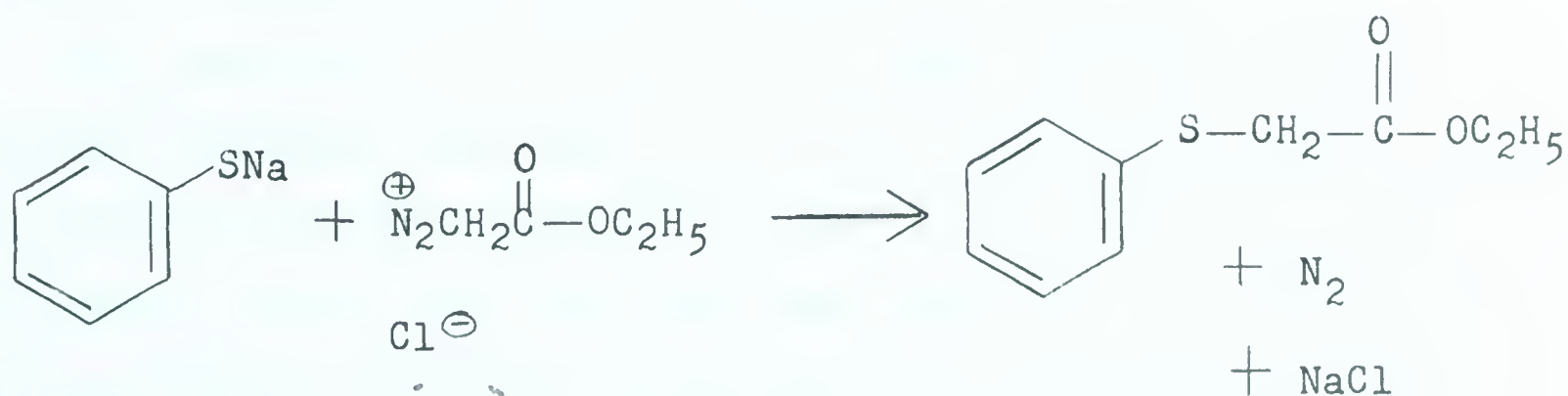




It should be emphasized that where aromatic systems are concerned, the above two methods of preparing thioethers (a, b, ), require an activated leaving group. Replacement of these groups can be accomplished only if there is an activating moiety, such as an electron withdrawing substituent ortho or para to the group being displaced in the aromatic system.

(c) Thioethers from Mercaptans and Diazo Compounds.

The methylation of mercaptans by diazomethane in ethereal solutions has met with limited success (10, 11, 12). However, diazoacetic acid ethyl ester, while unreactive towards mercaptans generally, reacts in good yield with highly acidic mercaptans such as thiophenol. By this method, S-phenylthioglycolic acid ethyl ester (XII), is produced in 81.6% yield from thiophenol and diazoacetic ester (13).



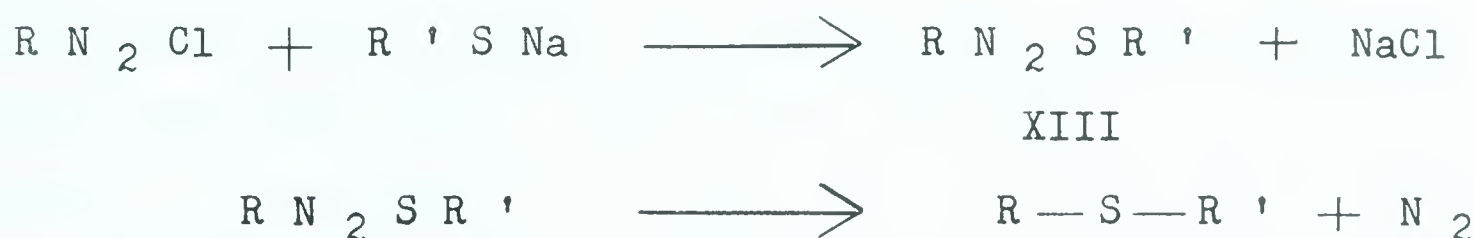
XII

The customary method to prepare aromatic thioethers is to treat the mercaptan with a diazotized amine in alkaline solution





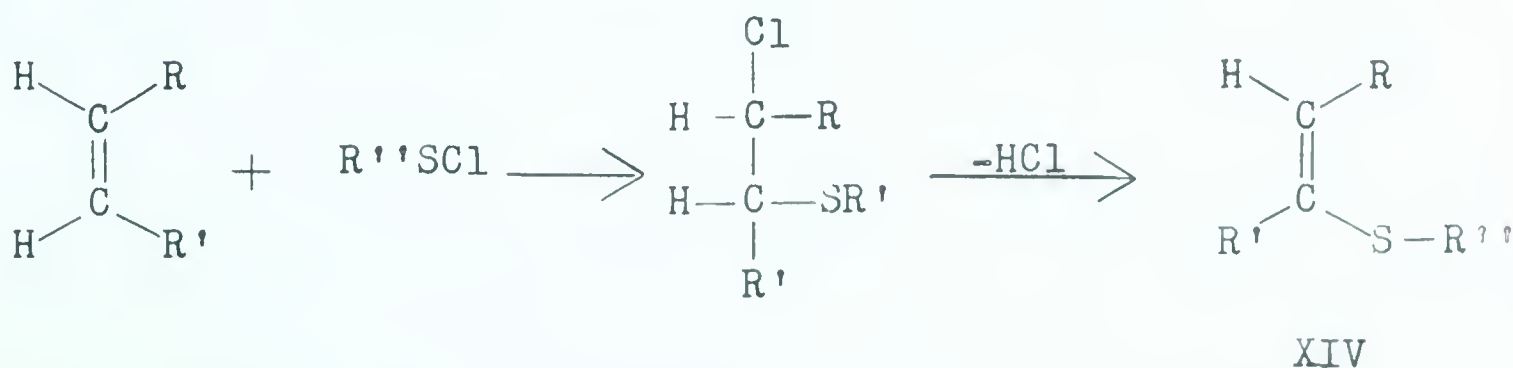
(14, 15, 16). The reaction gives, in the first step, an isolatable diazosulphide (XIII) which is often very stable, resisting change under week-long reflux. However, on occasion these diazosulphides rearrange explosively.



It should be pointed out that direct application of this method to an aminoindole would subject the indole system to a strongly acidic medium in the diazotization step. Difficulties would therefore arise, since indoles are known to yield dimeric and trimeric forms upon treatment with strong acids such as hydrochloric, hydrobromic or phosphoric acid (17, 18). These difficulties might be circumvented by the use of acetic acid.

#### (d) Thioethers from Sulfenyl Halides

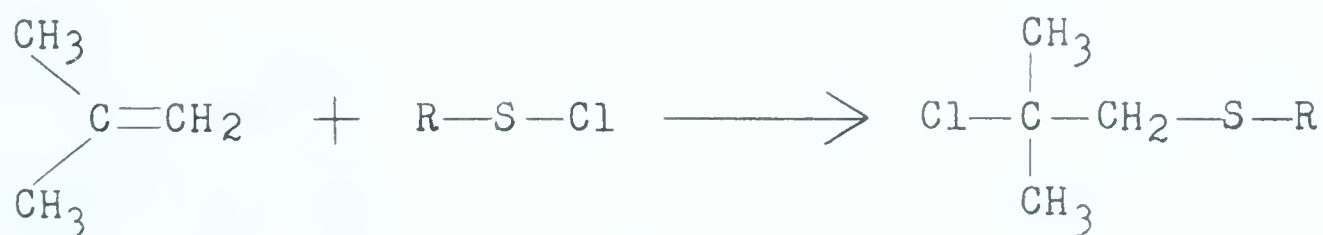
The preparation of  $\beta$ -chloroethyl aryl sulphides from sulfenyl chlorides and ethylene in carbon tetrachloride has been described (19). Cyclohexene and styrene have been shown to undergo similar addition reactions (20, 21). In some cases the preliminary addition is followed by a dehydrohalogenation (22), yielding an unsaturated thioether (XIV).





The general applicability of the reaction of sulfenyl halides with olefins has been described by R. A. Turner and R. Connor (23). In these studies, the extraordinarily stable sulfenyl chloride, 2-nitro-4-chlorobenzenesulfenyl chloride was used. In favourable cases the yields were almost quantitative. On the other hand yields were diminished or even non-existent where the carbon of the unsaturated group bore an electronegative groups such as phenyl or halogen. The same result was also observed when a carbonyl, carbethoxy or cyano group was attached to the carbon bearing the double bond.

In the case of the addition of sulfenyl halides to isobutylene (XV), the arylthio group adds to the carbon bearing the greater number of hydrogen atoms (24).



XV

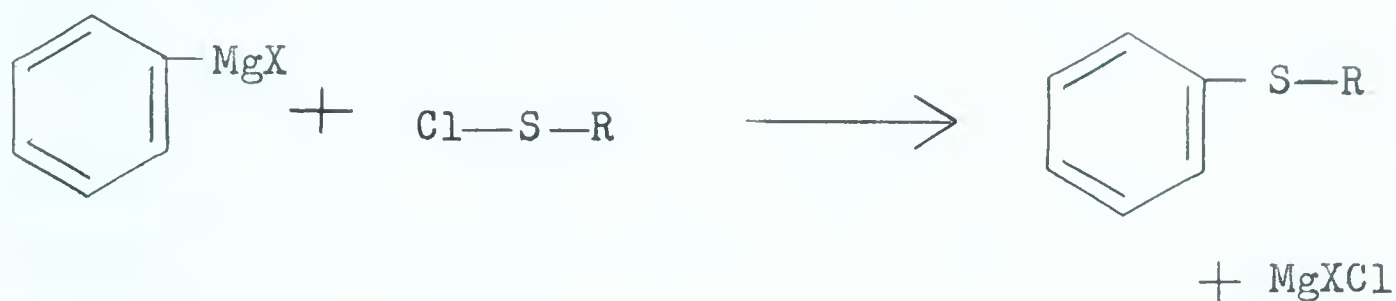
Acetylene has been shown (25), to undergo double addition upon treatment with chloromethylsulfenyl chloride, the product being  $\alpha,\beta$ -dichloro- $\alpha,\beta$ -bis-(chloromethylmercapto) ethane (XVI).



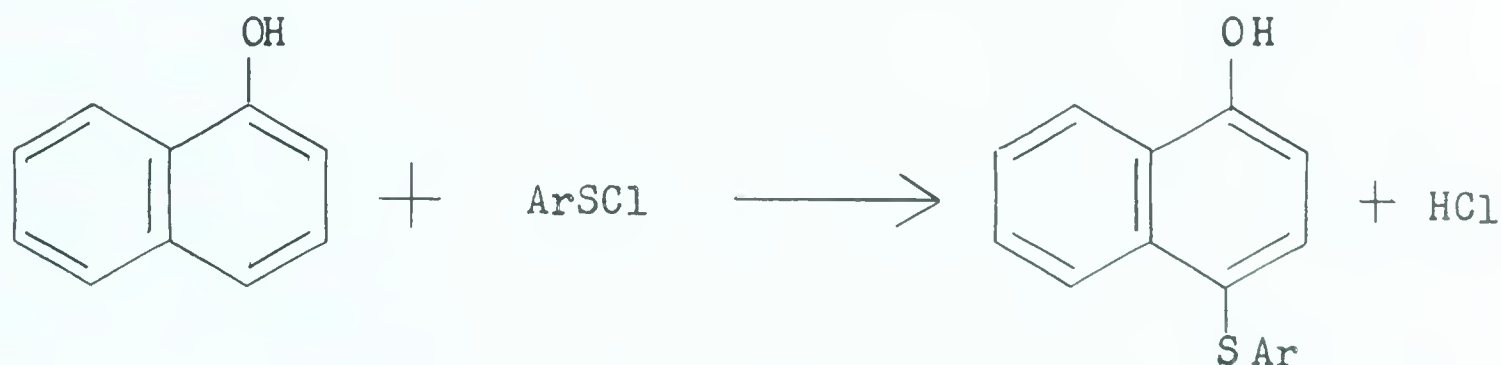
XVI



Sulfenyl chlorides are also known to react with Grignard reagents to yield the corresponding thioethers (26, 27, 28).



Thioethers are produced when aromatic sulfenyl halides, with or without catalysts replace hydrogen in suitably activated aromatic systems. Thus sulfenyl halides undergo coupling reactions with diazo compounds (29), and exhibit para substitution in phenols (30).



(B) Methods for the Introduction of Substituents at Position C<sub>3</sub> of the Indole Nucleus.

(a) Those involving substitution before the formation of the indole ring system.

1. Fischer Indole Synthesis.

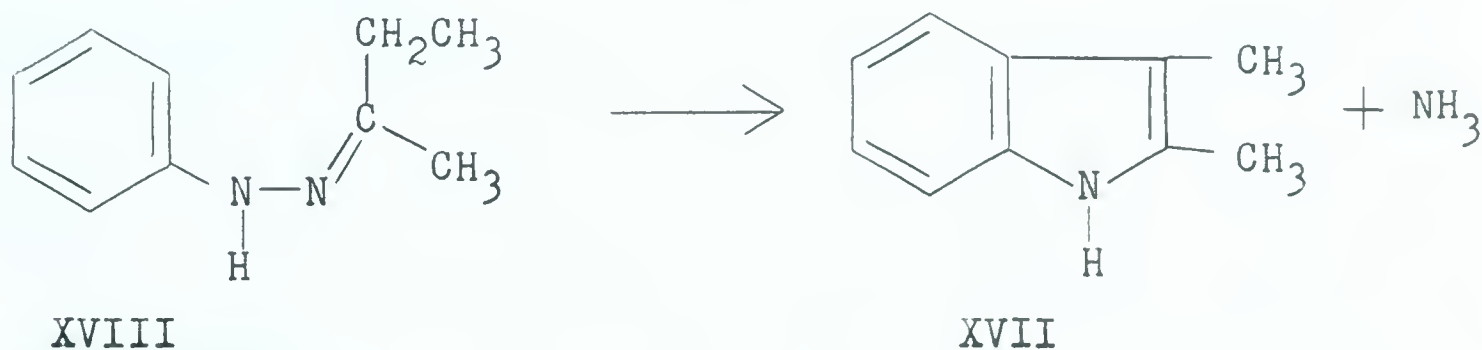
Of the many general synthetic methods developed to prepare indoles, that discovered by Emil Fischer (31) has proven to be



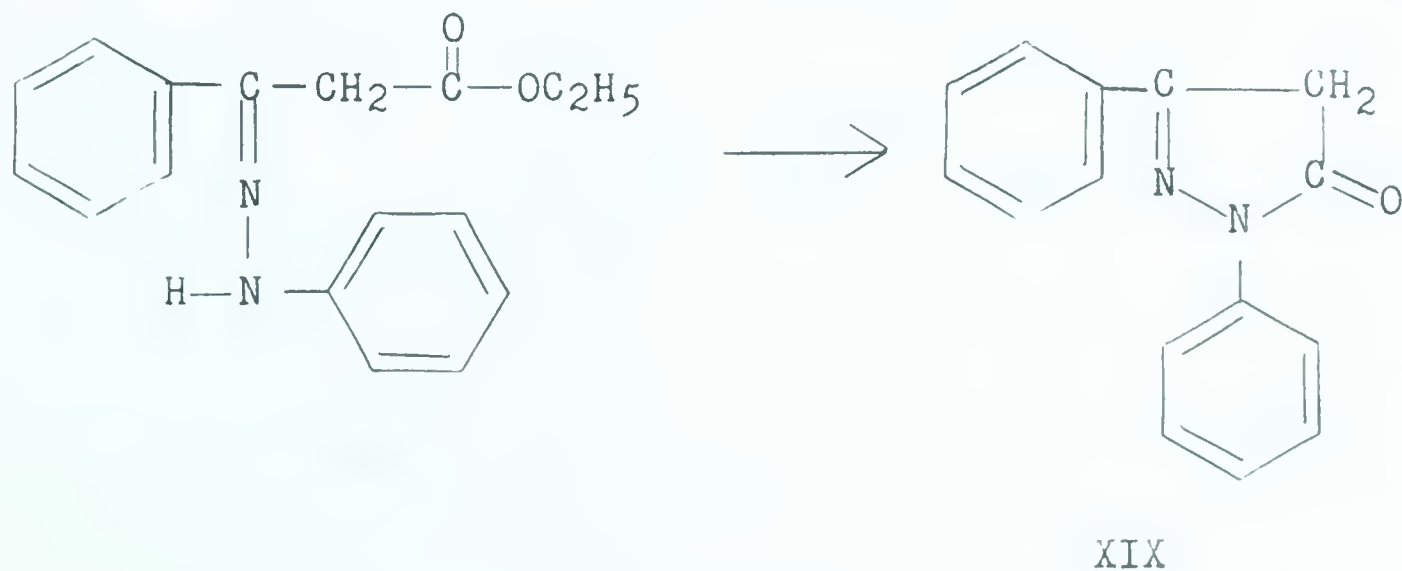


the most versatile. It is, in addition, the only procedure which readily lends itself to the formation of 3-substituted indoles.

Essentially, this method involves the formation of an indole with the liberation of ammonia from an arylhydrazone of appropriate structure, under the influence of an acid catalyst (32), or by the application of heat (33). The reaction may be illustrated by the formation of 2,3-dimethylindole (XVII), from the phenylhydrazone of methylethylketone (XVIII).

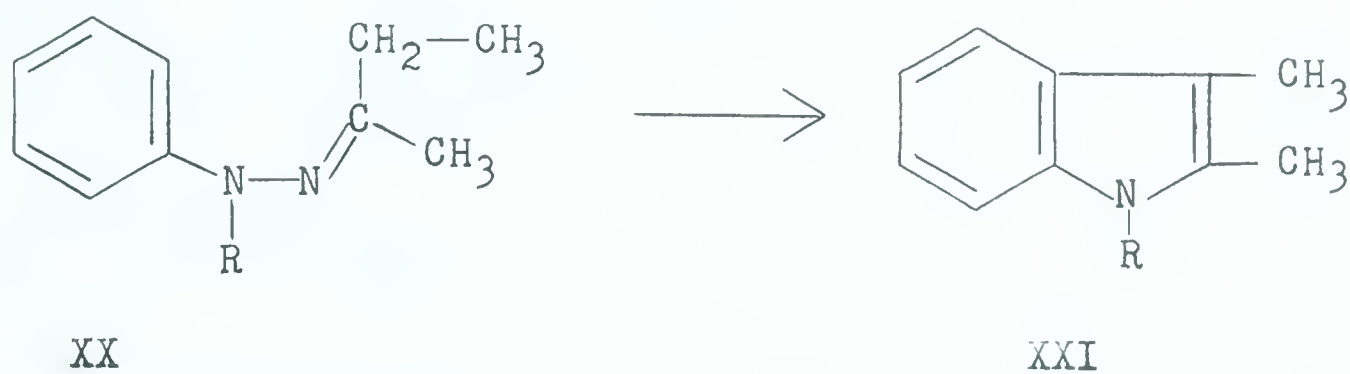


This reaction permits considerable variation in both the hydrazine and carbonyl compound involved. Although this synthesis enjoys considerable scope, certain limitations have been observed, other than those apparent from structural considerations: (i) Indole itself has eluded preparation from acetaldehyde phenylhydrazone (34). (ii) Pyrazolones (XIX) rather than the requisite indoles are generally produced from the phenyl-

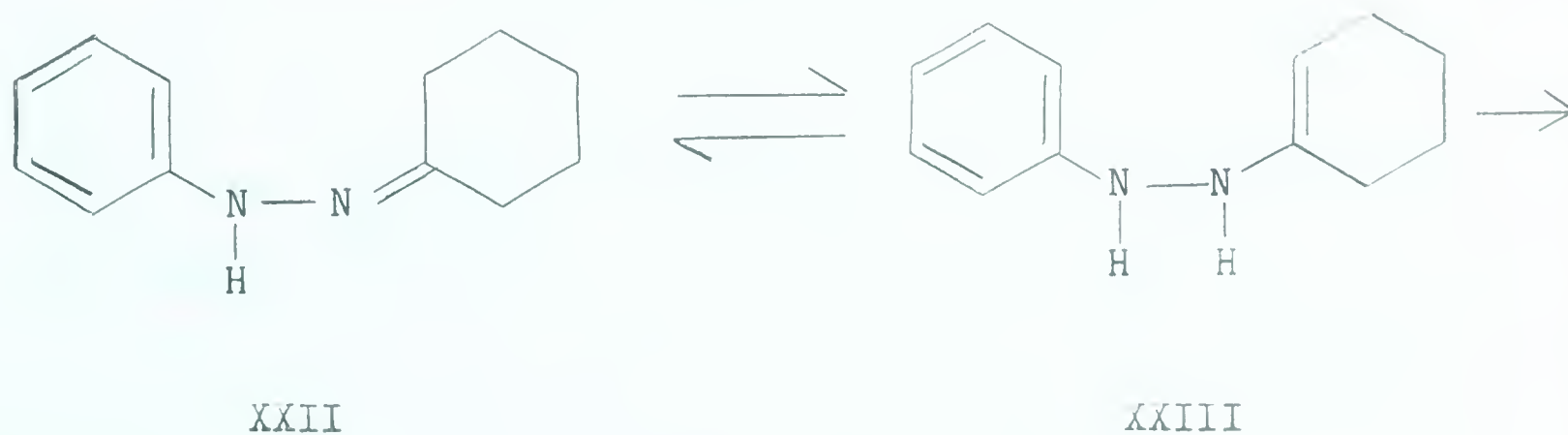




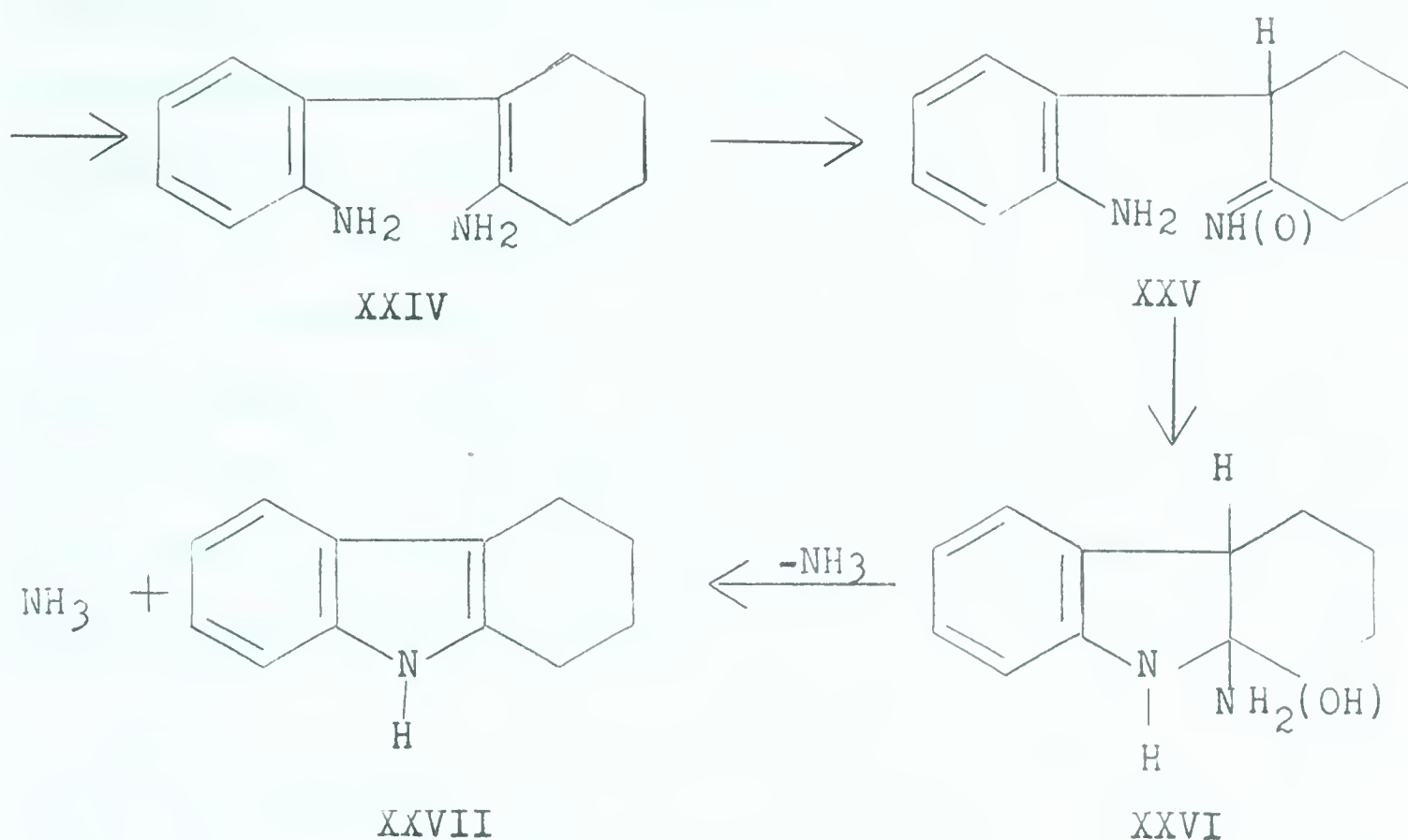
hydrazones of  $\beta$ -keto esters. (iii) In some instances a phenylhydrazone containing a free phenolic hydroxyl fails to undergo cyclization to the corresponding indole (35, 36). (iv) Although unsymmetrical ketones might be expected to yield a mixture of products, that indole is formed preferentially, in which the adjacent methylene is involved rather than the methyl group as shown by the conversion of (XX) to (XXI) (37).



The mechanism of the Fischer indole synthesis has been the subject of much research effort. The proposal of Robinson and Robinson (38) as modified by Allen and Wilson (39), has proven to be the most satisfactory explanation of the many facets of this reaction. The mechanism may be illustrated by the cyclization of cyclohexanone phenylhydrazone (XXII), as put forward in Elderfield's text on Heterocyclic Chemistry. (40).

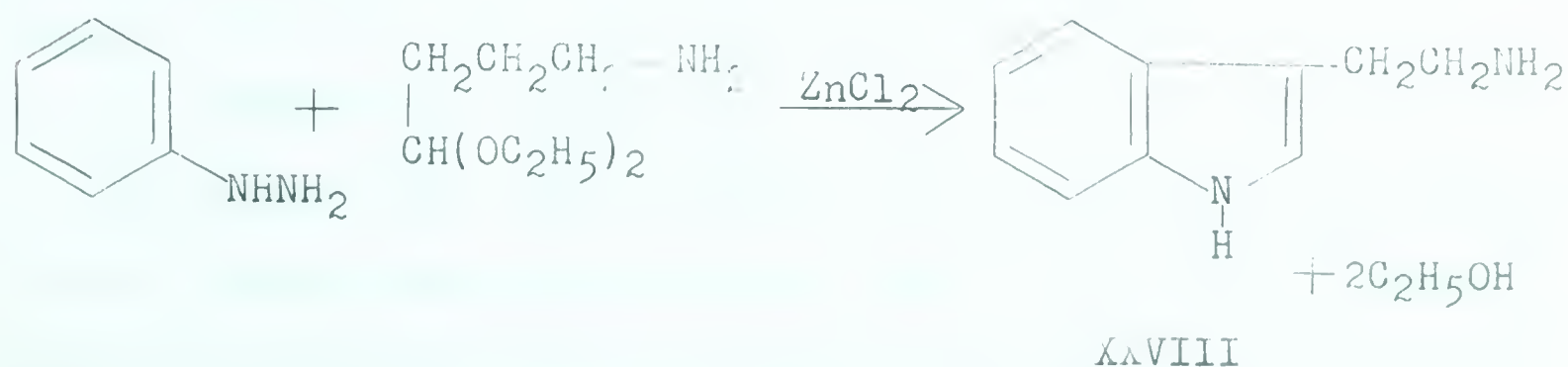






According to this mechanism the phenylhydrazone (XXII) in its tautomeric form (XXIII) undergoes an ortho-benzidine type rearrangement to the diamine (XXIV). The diamine, as the imine (XXV) or ketone (XXV, NH replaced by O), suffers an internal condensation yielding an indoline (XXVI) which loses a mole of ammonia to yield the indole (XXVII).

An interesting application of the Fischer indole synthesis in the preparation of 3-substituted indoles, is the first recorded synthesis of tryptamine, [3-(2-aminoethyl)-indole] (XXVIII).



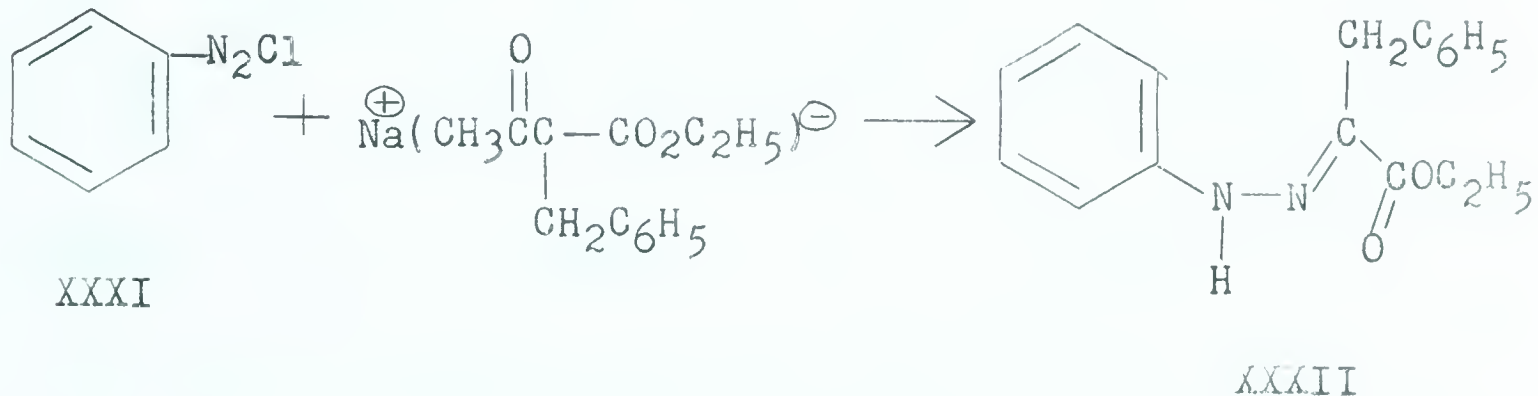
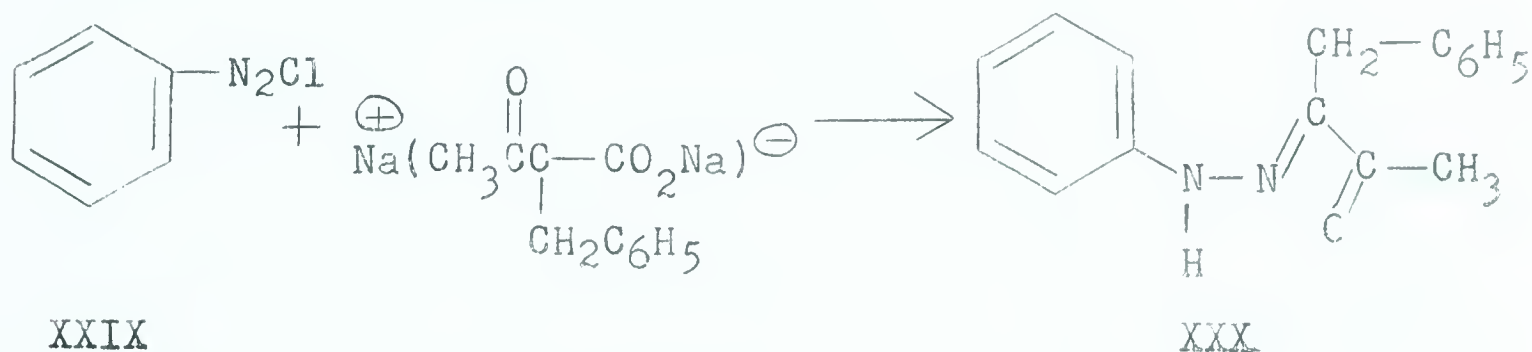




Treatment of a mixture of phenylhydrazine and  $\delta$ -aminobutyraldehyde diethyl acetal with anhydrous zinc chloride, afforded the requisite amino indole in 45% yield (41).

## 2. The Japp-Klingemann Synthesis.

A valuable adjunct to the Fischer indole synthesis is the Japp-Klingemann reaction. Its utility lies in the fact that the preparation of the necessary phenylhydrazones can be achieved from phenyl diazonium chlorides and the sodio derivatives of either  $\beta$ -keto acids or esters.



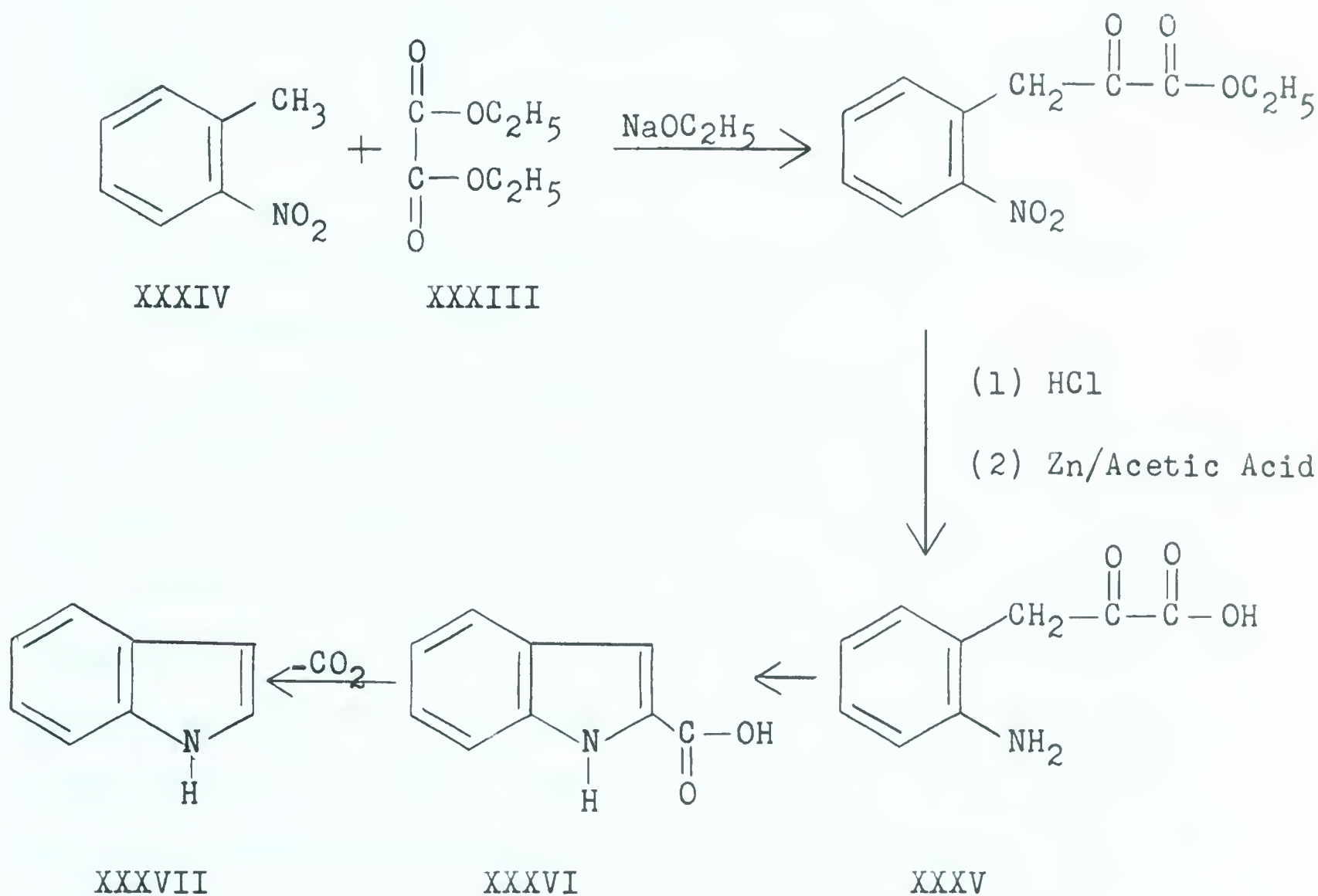
The conversion of (XXIX) to (XXX) proceeds with the loss of a carboxyl group, whereas in going from (XXXI) to XXXII) the reaction proceeds with the loss of an acyl group.

## 3. The Reissert Synthesis.

The method devised by Reissert (42) in 1887 for the preparation of indole from o-nitrotoluene has been modified by Kermack, Perkin and Robinson (43) to include the preparation of certain



3-substituted indoles. Reissert's original synthesis involved an initial condensation of diethyl oxalate (XXXIII) with o-nitrotoluene (XXXIV) in the presence of sodium ethoxide in anhydrous ether.

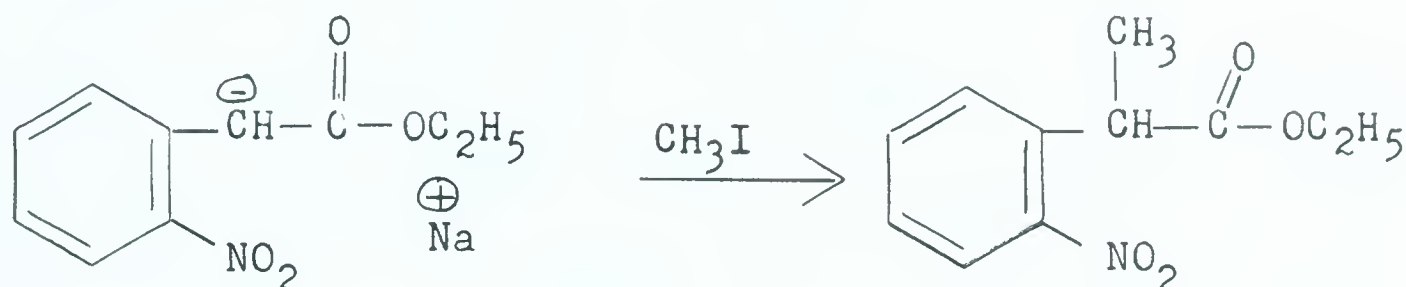


The ethyl o-nitrophenylpyruvate was hydrolysed and reduced with zinc in acetic acid to the intermediate o-amino-phenylpyruvic acid (XXXV), which cyclized under the reaction conditions to indole-2-carboxylic acid (XXXVI). Pyrolysis of the acid (XXXVI) produced indole (XXXVII), with the elimination of carbon dioxide.

By substitution of the appropriate group on the methylene unit of the phenylpyruvic acid ester (e.g. methyl as shown



below) it is possible to make 3-substituted indole structures by this reaction.

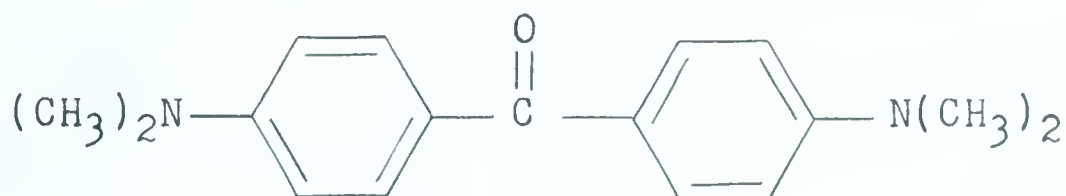


(b) Those methods involving substitution at  $\text{C}_3$  after formation of the indole ring system.

1. The use of indolylmagnesium halides.

A general method to obtain 3-substituted indoles lies in the many and varied reactions of the indolylmagnesium halides.

Indole reacts with Grignard reagents to yield indolylmagnesium halides (44). These derivatives are frequently regarded as being the  $\text{>N-Mg-X}$  derivatives (45), although the alternative  $\text{>C}_3\text{-MgX}$  configuration has been suggested (46). The fact that pyrrolylmagnesium halides (regarded as  $\text{>C}_3\text{-MgX}$  derivatives) react with Michler's ketone (XXXVIII), while indole derivatives do not, is regarded as evidence of N substitution.



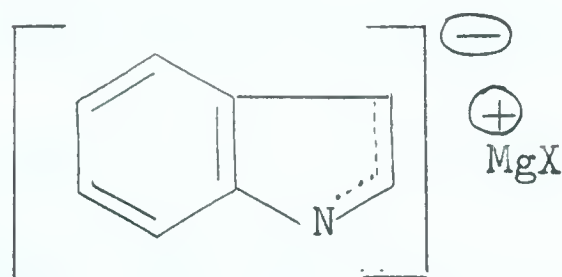
XXXVIII

Recent Nuclear Magnetic Resonance and Infra Red spectroscopic investigations carried out on the indole Grignard reagent





(47), indicate that this complex is best represented as the ionic hybrid (XXXIX).

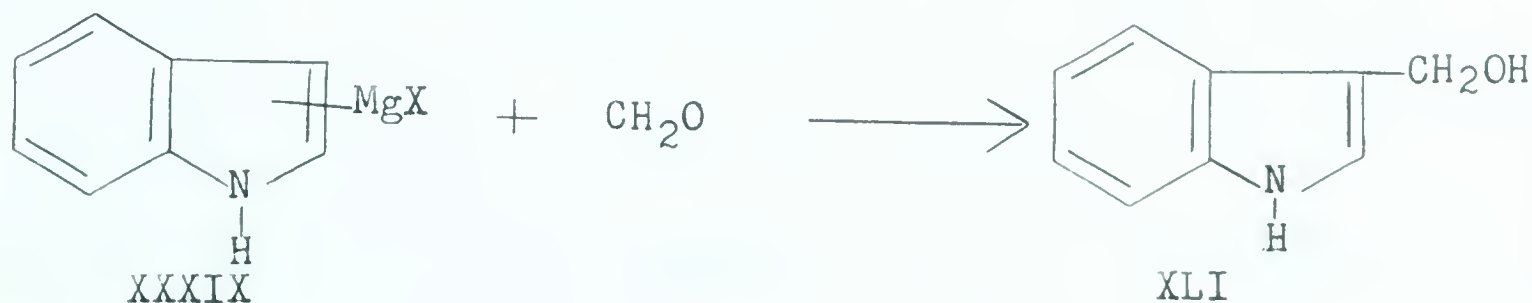
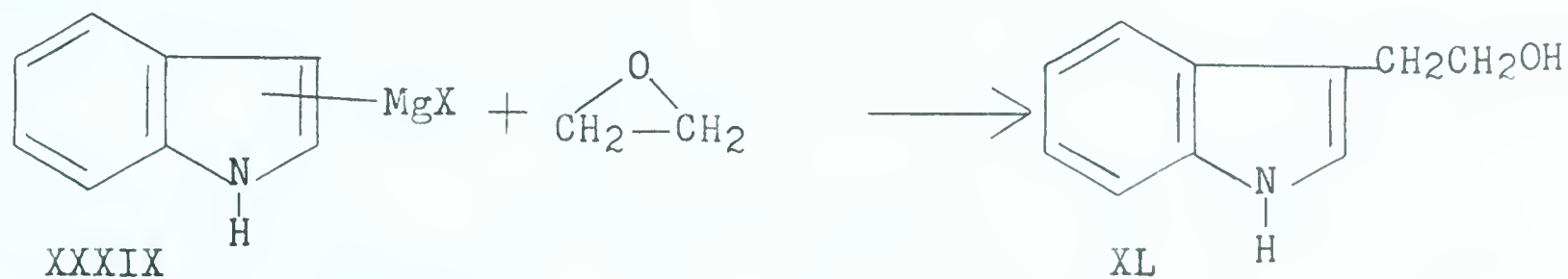


XXXIX

Indolylmagnesium iodide reacts with methyl iodide to yield 3-methylindole and 1-methylindole. Prolonged heating appears to favour substitution at C<sub>3</sub> (48).

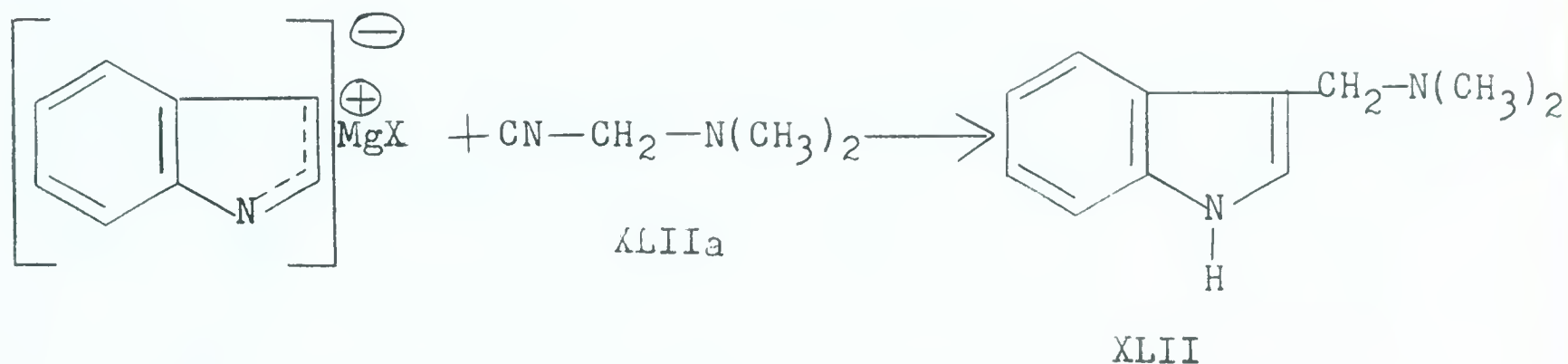
Indolylmagnesium halides react in general with carbon dioxide at low temperatures to yield the rather unstable indole-1-carboxylic acids. At higher temperatures, the 3-carboxy derivative predominates (49, 50). The compound 2-methylindole reacts similarly to yield both the 1- and 3-methylated derivatives (51).

Indolylmagnesium halides react with ethylene oxide and with formaldehyde in the usual manner (52, 53), as shown below, in the conversion of the structures (XXXIX) to (XL) and (XXXIX) to (XLI).





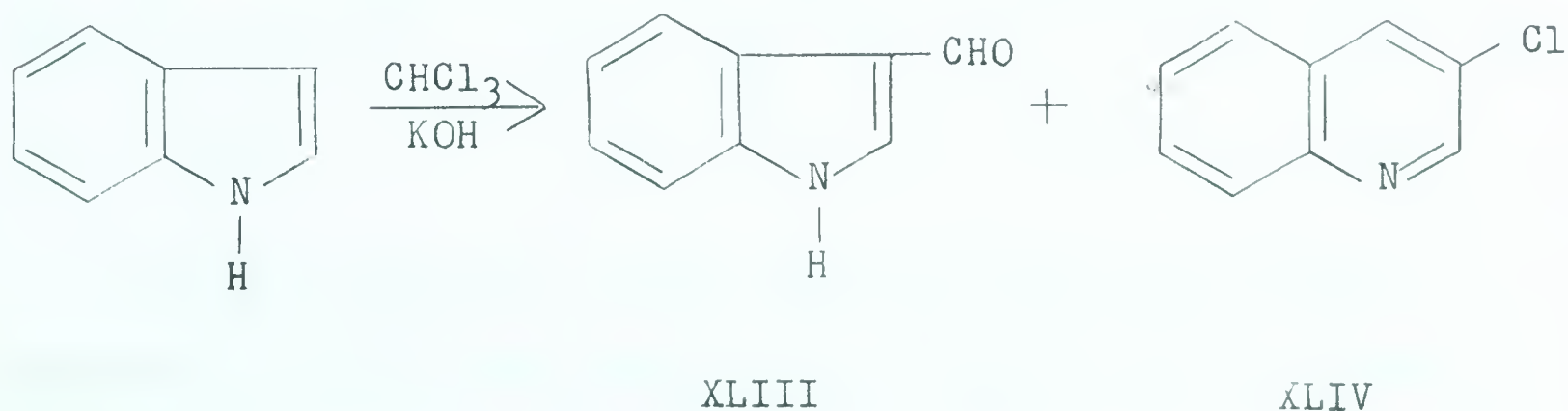
The synthesis of gramine, (3-[dimethylaminomethyl]-indole) (XLII), from dimethylaminoacetonitrile is a further demonstration of the versatility of indolylmagnesium halide (54).



The reaction of the latter with (XLIIa) yields the desired amine by displacement of the cyano group. This is in distinct contrast to the behaviour of indolylmagnesium iodide with chloroacetonitrile, a reaction in which the halogen atom is preferentially displaced (55).

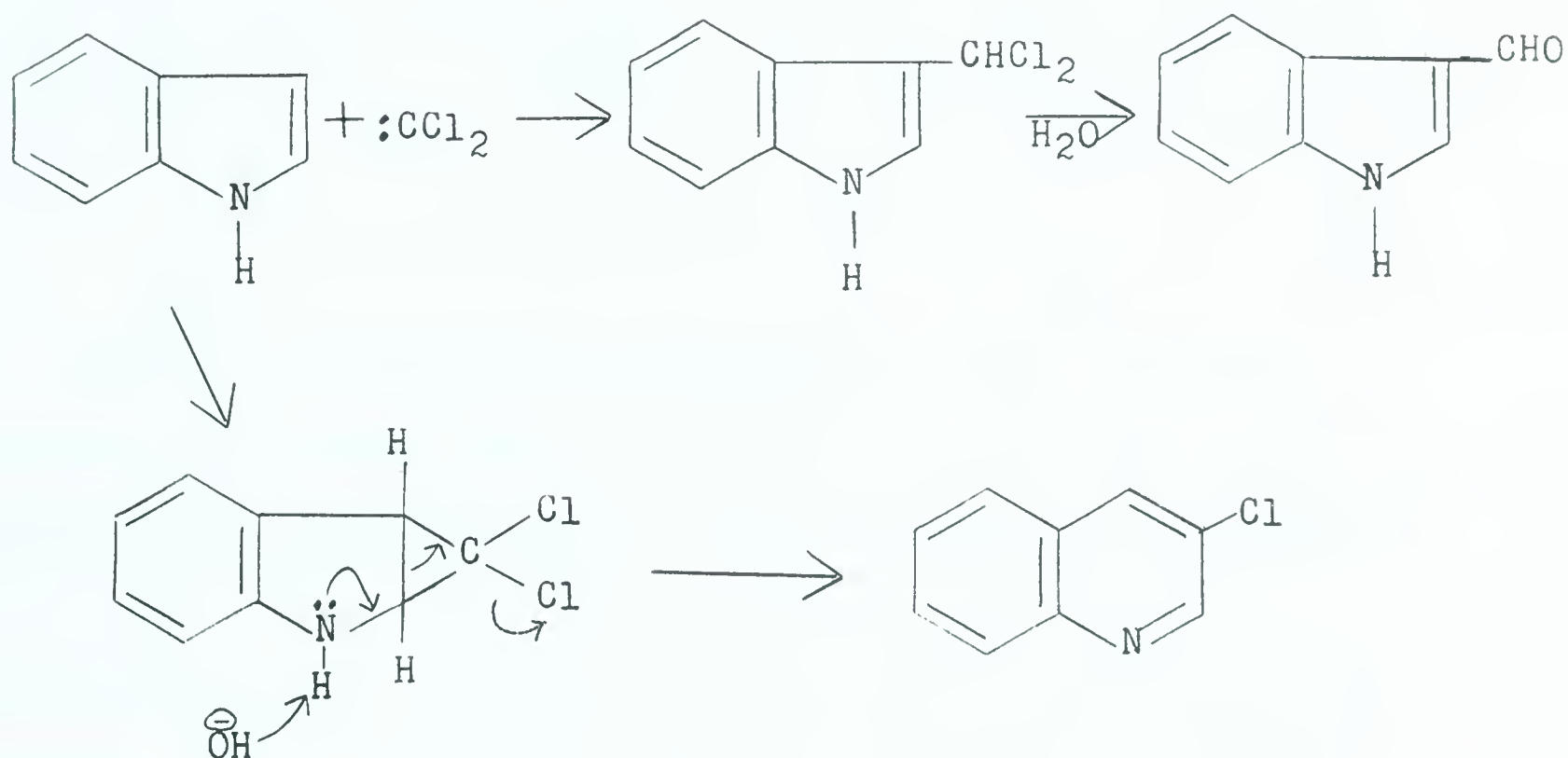
## 2. Condensations resulting in 3-indolyl compounds.

The application of the Reimer-Tieman synthesis to indole leads to the formation of 3-indolecarboxaldehyde (XLIII). The compound  $\beta$ -chloroquinoline (XLIV) is also a product of this reaction and is postulated to arise from an addition of dichlorocarbene, generated by the action of base with chloroform,

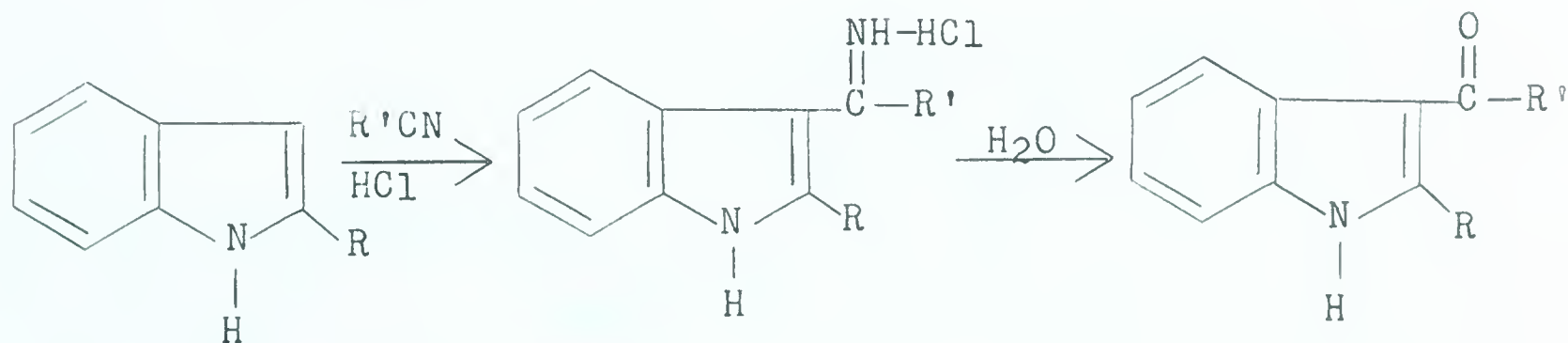




to the 2,3 double bond of indole (56) as illustrated below.



The Houben-Hoesch synthesis has been applied to the synthesis of 3-indolyl ketones (57). Thus, nitriles in the presence of hydrogen chloride, react with indoles to yield the corresponding ketones.

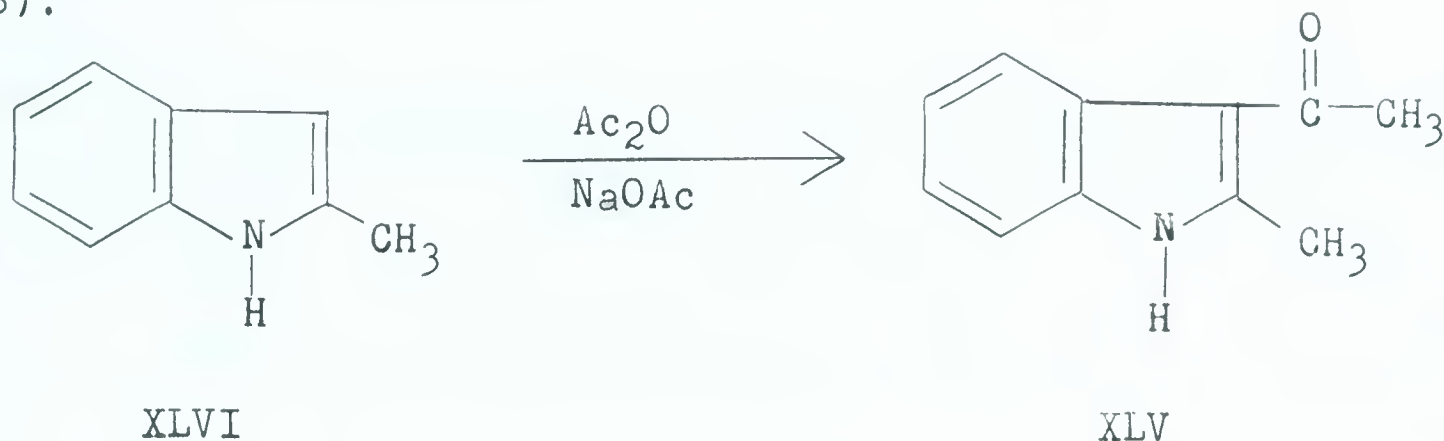


In some instances, indoles react directly with acetic anhydride to yield the corresponding 3-indolyl methyl ketone.

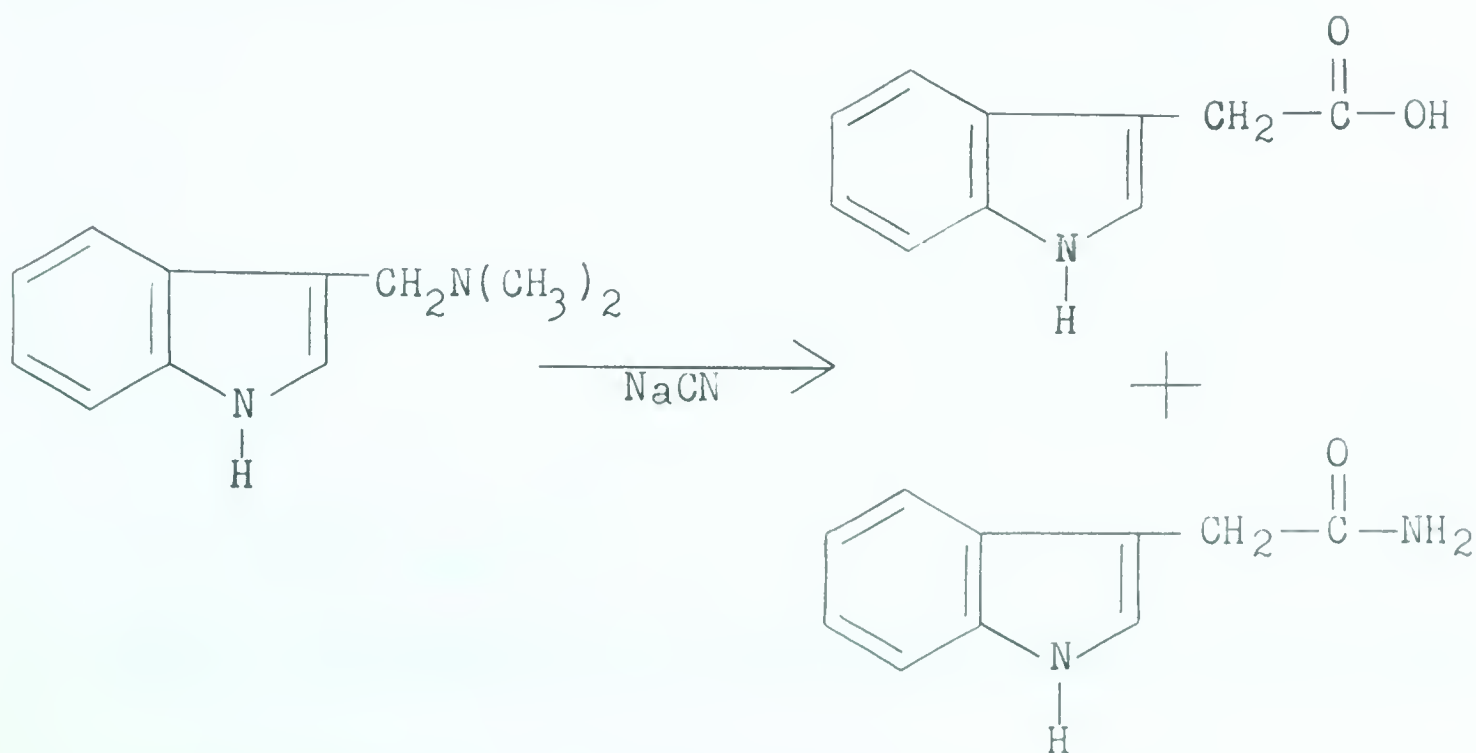




In this way 2-methyl-3-indolyl methyl ketone (XLV), has been prepared in an 80% yield by the treatment of 2-methylindole (XLVI) with acetic anhydride in the presence of sodium acetate (58).

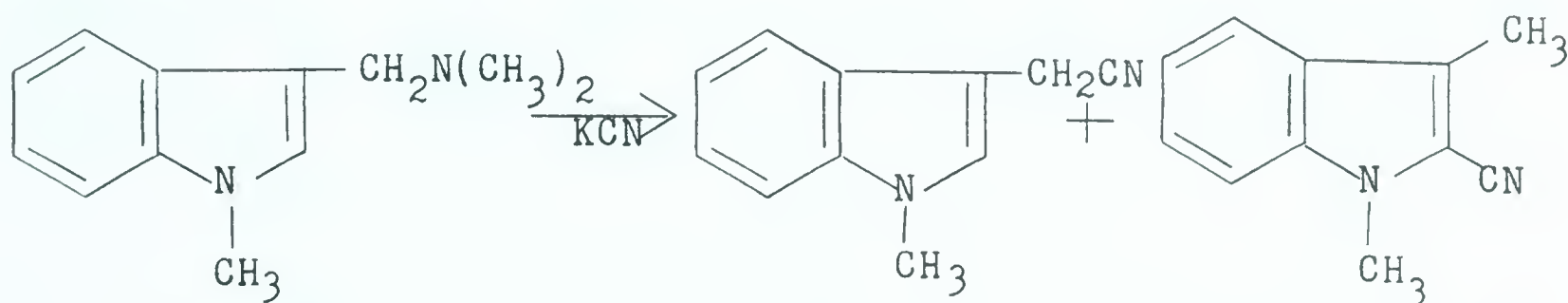


Gramine, an important intermediate in many synthetic sequences, is conveniently prepared by the Mannich reaction involving the reagents indole, formaldehyde and dimethylamine (59). The utility of gramine, or its derivatives may be exemplified by the following reactions which these compounds undergo. Thus 3-indoleacetic acid is produced in excellent yield when gramine is treated with sodium cyanide. This is the cleanest preparation of 3-indoleacetic acid on record (60), the overall yield being close to 90% (including the product obtained from hydrolysis of the amide which is also formed).

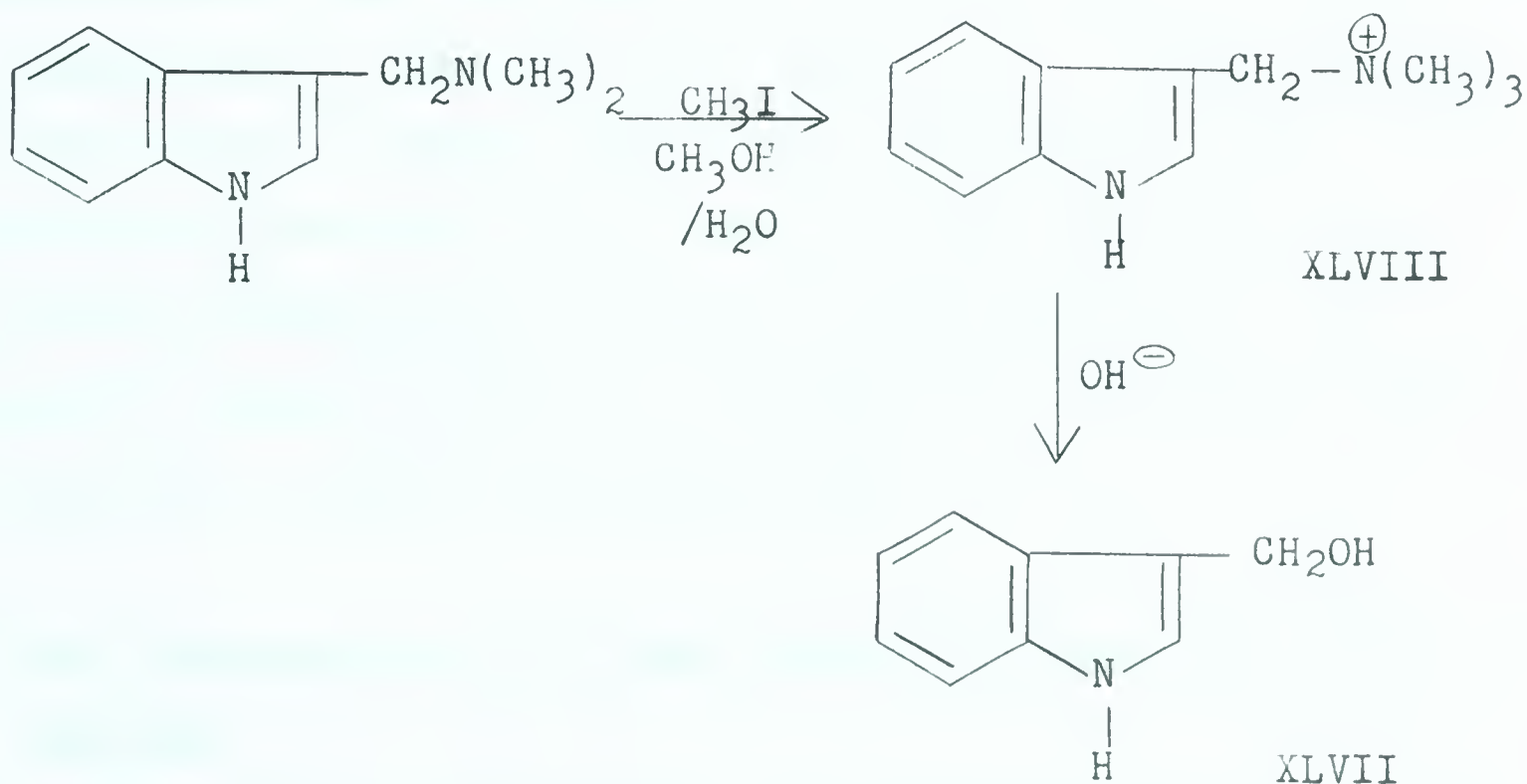




Similarly, 1-methylgramine has been treated with potassium cyanide, the products of the reaction being the desired nitrile along with some 1-methyl-2-cyanoskatole (61).



As a final example, 3-hydroxymethylindole (XLVII) is produced when gramine is treated with methyl iodide in aqueous methanol (62). The first step in the reaction is no doubt the formation of the quaternary ammonium salt (XLVIII), which suffers displacement of the trimethylamine by the hydroxide ion.

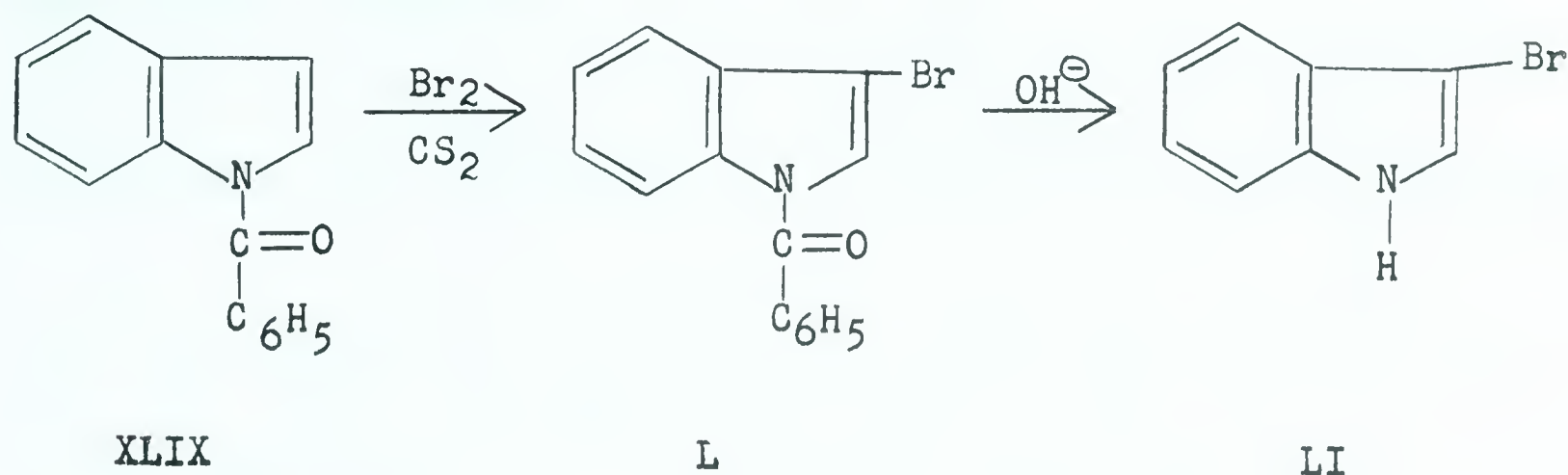


### 3. 3-Halo Indoles.

Direct halogenation of N-acetylated indole takes place with



exceptional ease. The N-acyl-3-haloindole is then readily hydrolysed to the corresponding 3-haloindole. Thus, treatment of N-benzoylindole (XLIX) with bromine in carbon disulfide yields



N-benzoyl-3-bromoindole (L) which can subsequently be hydrolysed to 3-bromoindole (LI) in 55% overall yield (63). The preparation of 3-chloroindole has been accomplished in a similar manner (63). The action of sulfuryl chloride on indole is reported to yield 3-chloroindole (64), although other workers report the formation of 2-chloroindole with the same reagent (65). Dioxan dibromide has been used to convert indole into 3-bromoindole (66). Indole has been reported to undergo transiodination reactions with 4-iodo-2,6-dimethylphenol yielding 3-iodoindole (67). The action of iodine on indole in the presence of potassium iodide is reported to yield 3-iodoindole (68).

### (C) The Determination of 2- and 3-Substitution in the Indole Nucleus.

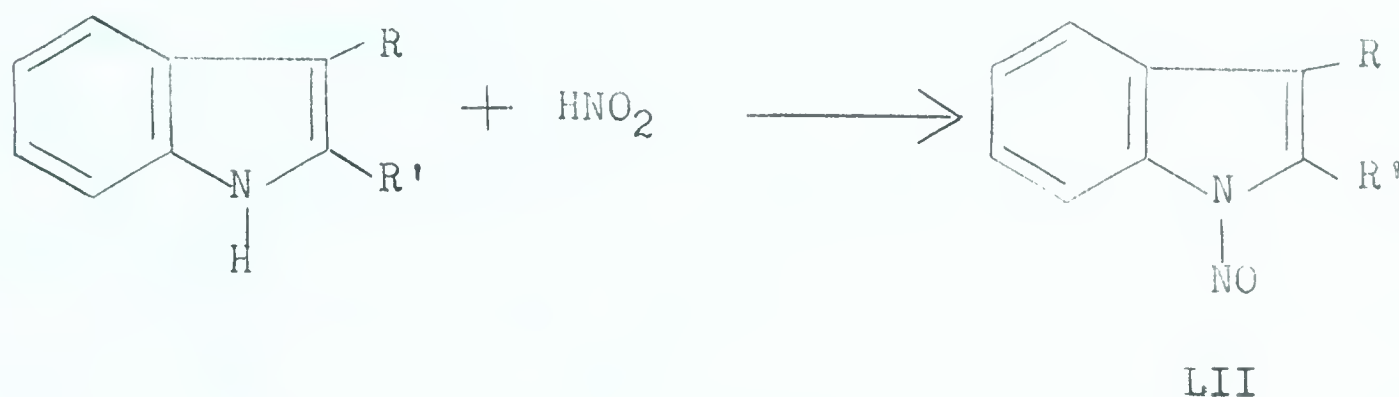
Prior to the present work, the literature reports only one method useful in the determination of substitution in the pyrrole portion of the indole ring system. This is a chemical method





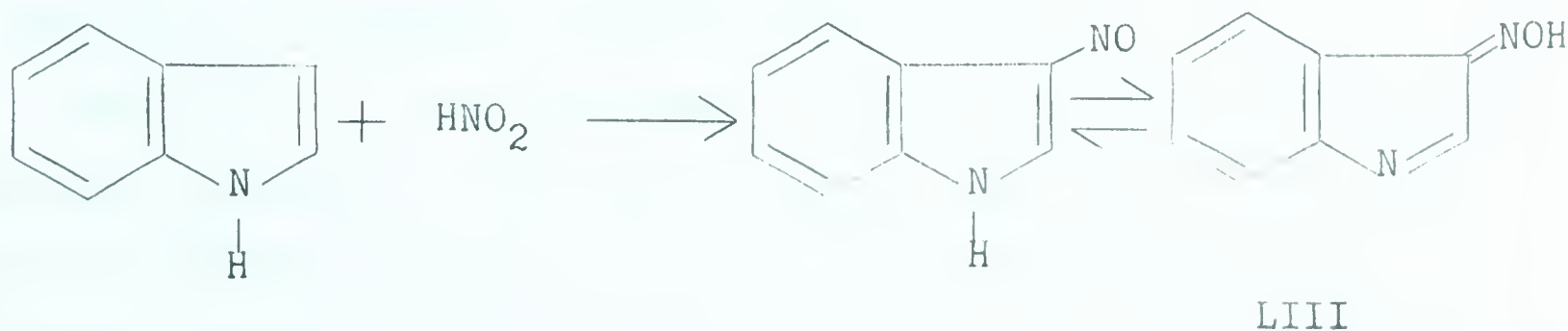
which was developed by Verkade, Lieste and Werner (69).

These authors found that the reaction of substituted indoles with nitrous acid can be used to determine the position of substitution in the pyrrole ring of indole. Indole derivatives substituted in the 3, or 2 and 3 positions yield N-nitroso derivatives (LII), according to the scheme below. These N-nitroso



derivatives are insoluble in base (in the absence of a carboxyl group in the indole nucleus). They also exhibit a positive Liebermann reaction (70), and undergo coupling reactions with diphenylamine.

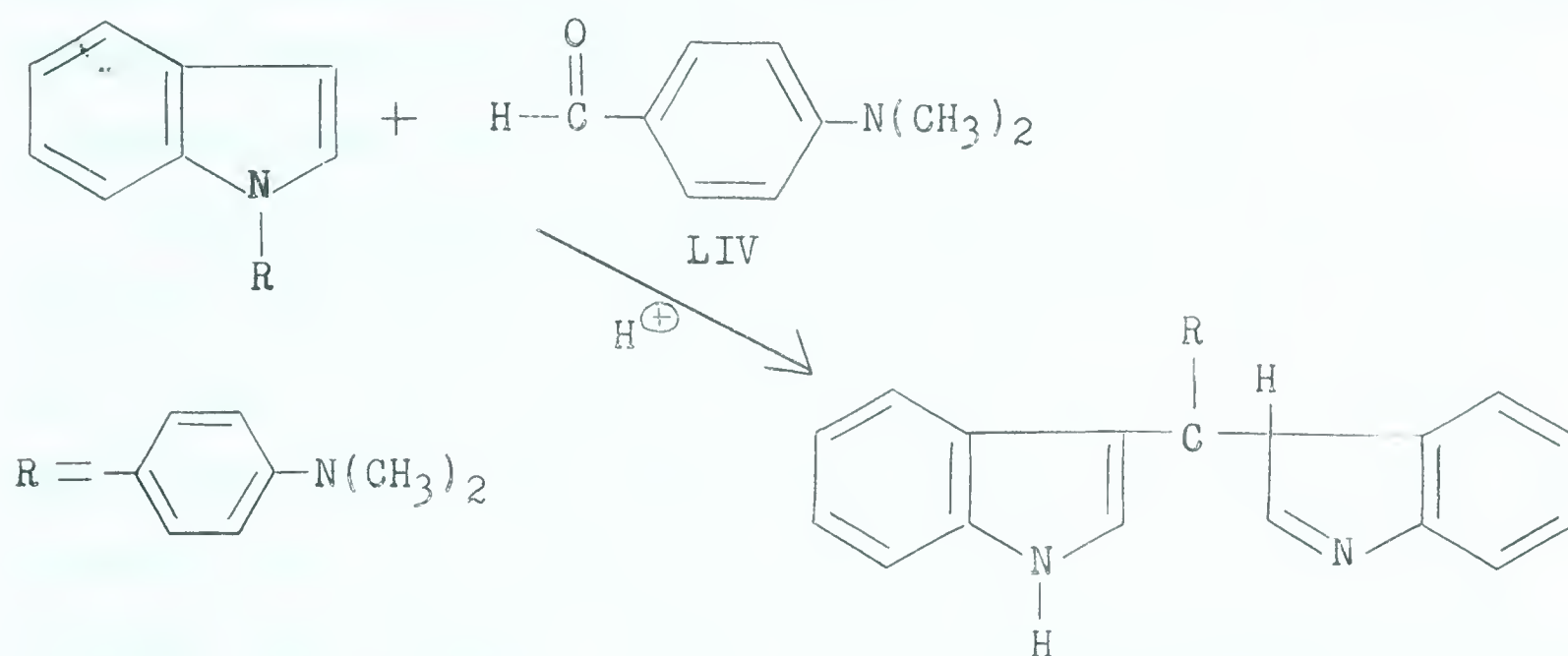
On the other hand, indole derivatives with a free C<sub>3</sub> position yield 3-isonitroso derivatives (LIII), which are soluble in potassium hydroxide with simultaneous production of a red colour, and are unreactive towards Liebermann's reagent or to diphenylamine. Those indoles substituted in either the 1,3 or the 1,2





and 3 positions do not undergo reaction with nitrous acid, while those substituted in the 1 and 2 positions yield nitroso derivatives which are insoluble in base, and do not undergo reactions with the above reagents.

In this connection, mention should be made of the reaction discovered by Ehrlich (71). He discovered that p-dimethylaminobenzaldehyde (LIV) reacts with indoles having a free 2 or 3 position to yield derivatives of characteristic colour, red through blue.



This colour, the basis of a colorimetric procedure for the estimation of indoles, was found to be due to the formation of a rosindole (71).

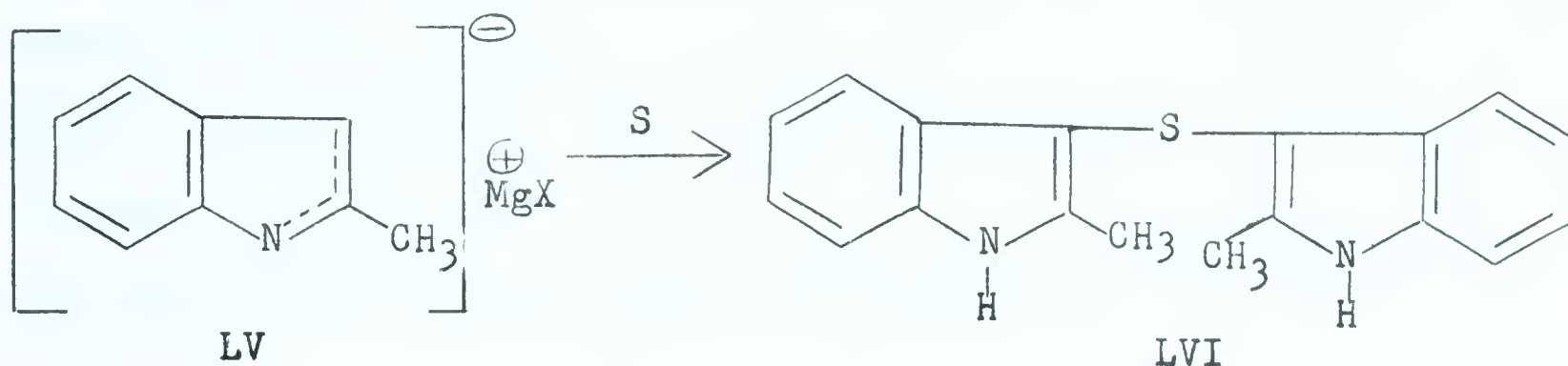
p-Dimethylaminobenzaldehyde reacts readily with indoles at the 3 position, in preference to reaction at position  $\text{C}_2$ . Strongly acidic conditions however promote reaction at  $\text{C}_2$  (72).

#### D. Reported Preparation of Indolyl Thioethers.

The first published account of the preparation of an indolyl thioether appeared in 1915 when Madelung and Tencer (73) synthesized diindolyl sulphide from indolylmagnesium bromide and sulphur. These authors found in addition that 2-methylindolylmagnesium bromide (LV) on treatment with sulphur, formed 2,2'-

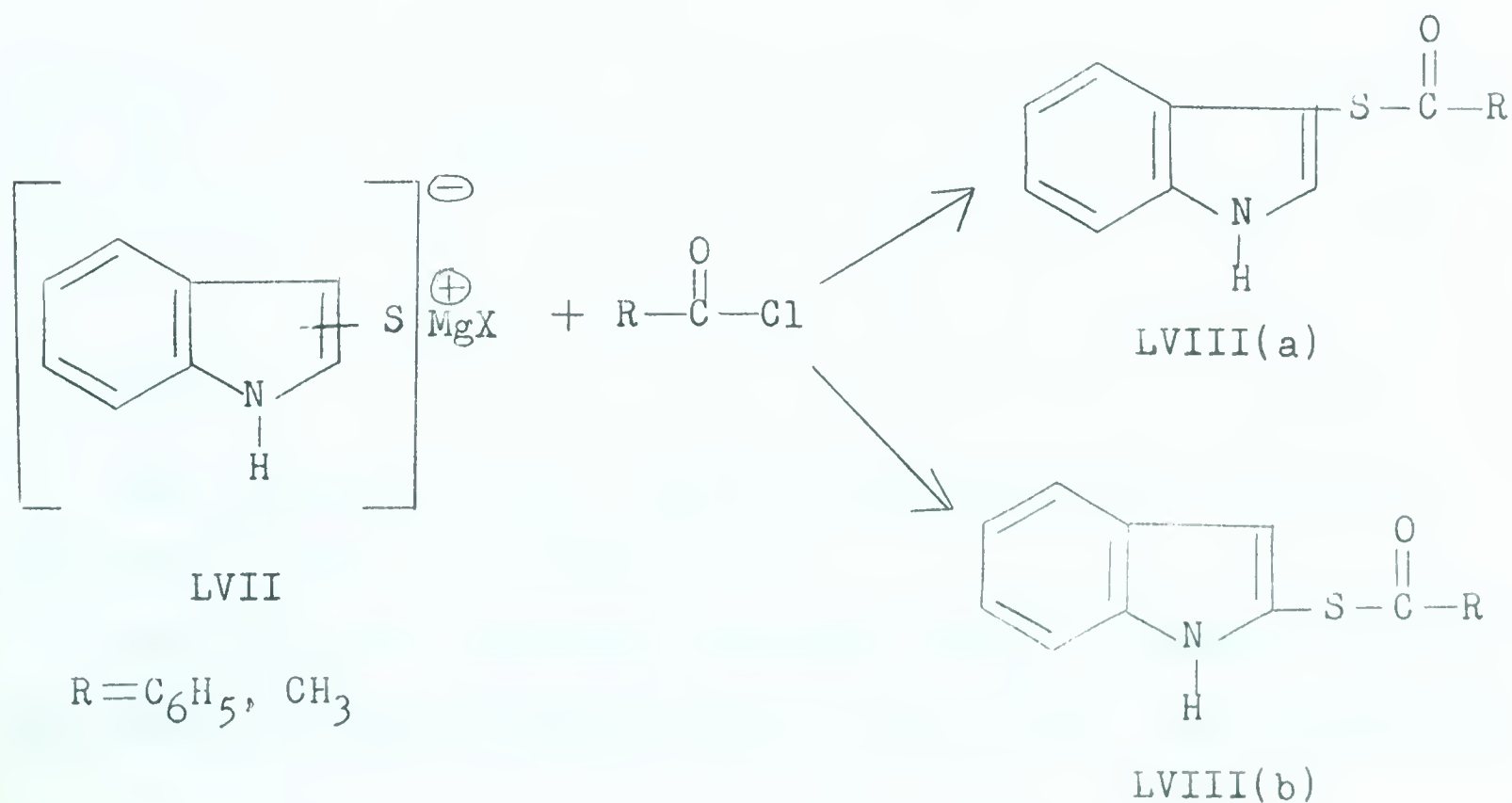


dimethyl-3,3'-diindolyl sulphide (LVI).



Oddo and Mingoa (74) obtained similar results by the reaction of sulphuryl chloride or sulphur dioxide with the indole Grignard reagent and regarded these compounds as the 3,3'-diindolylsulphone and 3,3'-diindolylsulphoxide respectively.

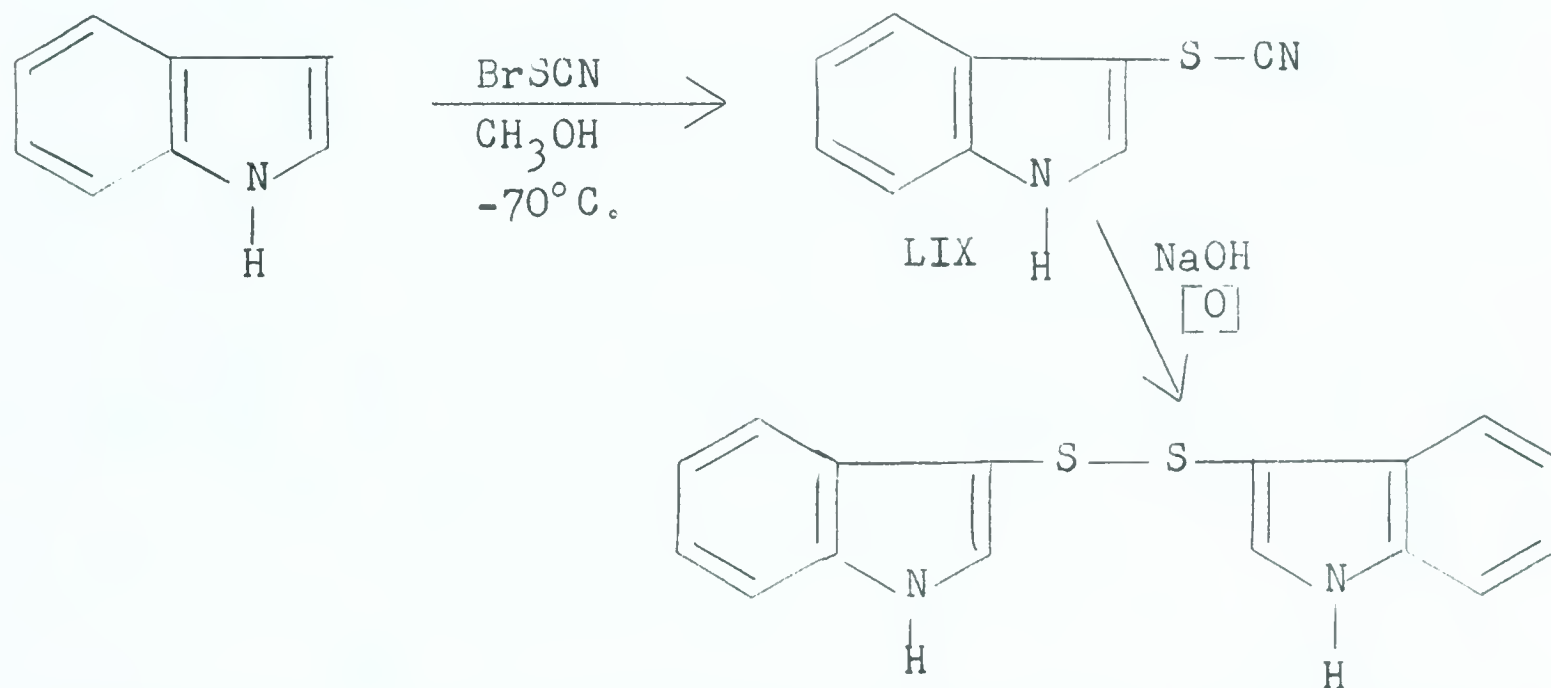
Oddo and Mingoa extended the reactions of indolylmagnesium halides and sulphur to the preparation of what they considered to be the 2- and 3-indolyl thioesters and 2- and 3-indolyl mercaptans (75). Thus, indolylthiomagnesium halides (LVII) when treated with acyl halides were reported to yield thioesters (LVIIIa) and (LVIIIb). These esters were subsequently hydrolysed to provide the corresponding mercaptans.



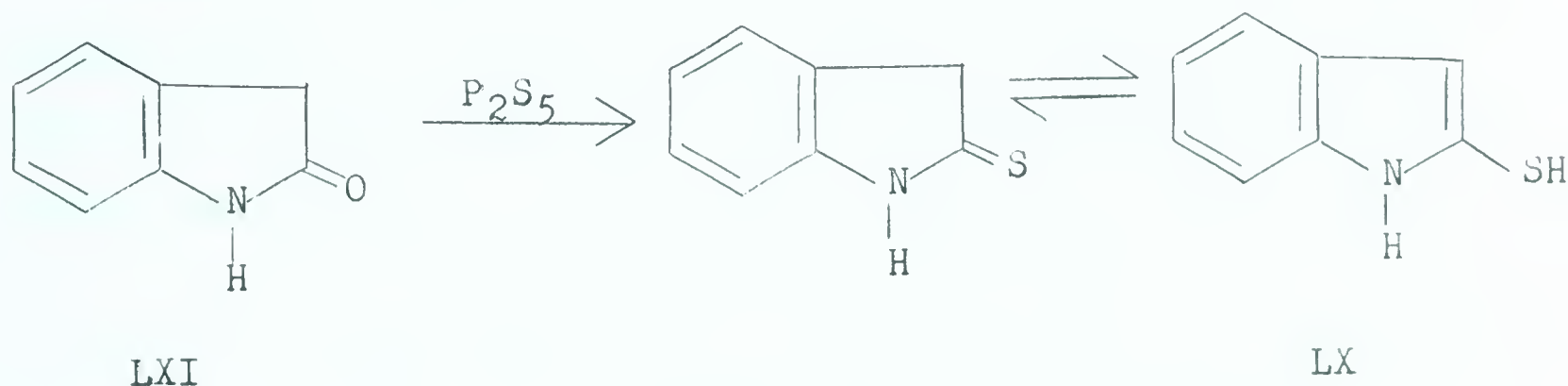




Recently Snyder and Grant have pointed out the similarity between the melting points of their 3,3'-diindolyl disulfide, and Oddo's 3-mercaptoindole (76). Snyder and co-workers actually had obtained 3,3'-diindolyl disulfide by the thiocyanation of indole followed by hydrolysis of the 3-thiocyanoindole (LIX).



2-Mercaptoindole (LX) has also been prepared by Sugasawa (77) by the action of phosphorus pentasulphide on oxindole (LXI) in xylene.

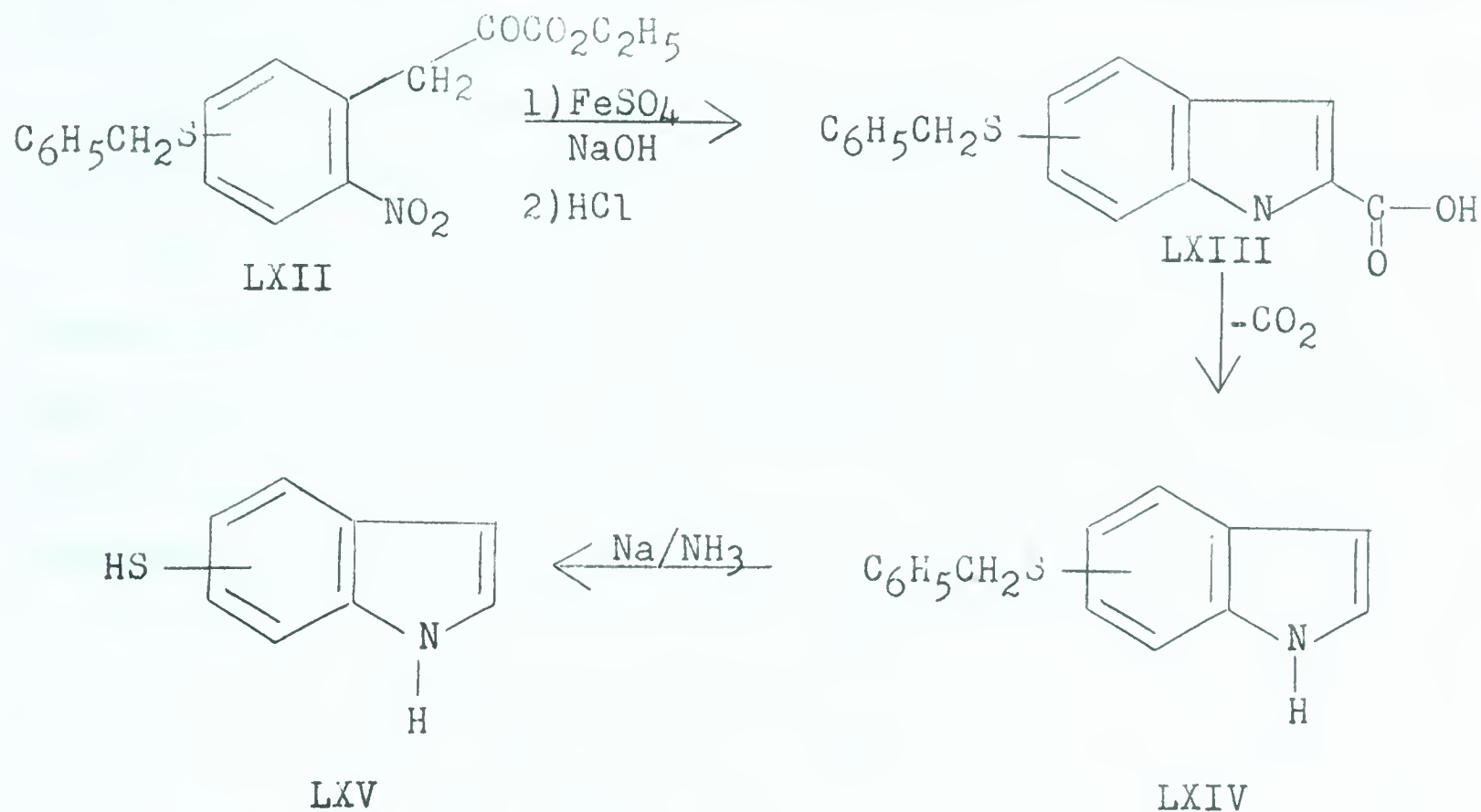


The melting point of 2-mercaptoindole reported by Oddo is  $148-150^\circ\text{C}$ ., that by Sugasawa  $145^\circ\text{C}$ .

Utilizing the Reissert synthesis, Piers, Haarstad, Cushley and Brown (78) have prepared the 4-, 5-, 6- and 7-benzylmercapto-

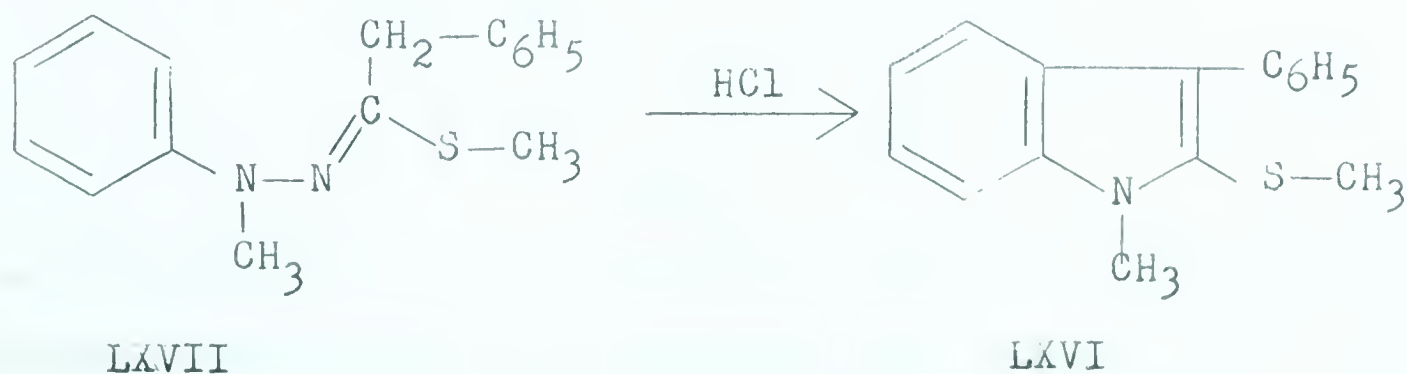


indoles. The appropriate benzylthionitrotoluene (LXII) was cyclized to the corresponding benzylthioindole-2-carboxylic acid (LXIII), which was decarboxylated in quinoline to the benzylthio-



indole (LXIV). The thio ether was subsequently reductively cleaved by sodium in liquid ammonia, to yield the corresponding mercaptoindole (LXV).

The Fischer indole synthesis has been successfully applied in the synthesis of 1-methyl-2-methylthio-3-phenylindole (LXVI) (79) by the cyclization of a S-methyl thiophenylacetic acid  $\alpha$ -N-methylphenylhydrazide (LXVII) in the presence of hydrochloric

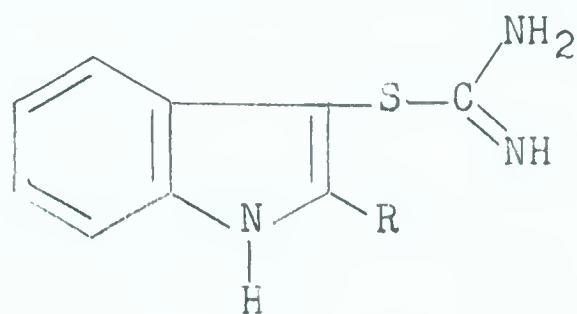




acid. This reaction was also observed when the  $\beta$ -methyl group was replaced by a mercapto group. It has been found however, that the  $\alpha$ -N-methyl function is a structural necessity in this particular cyclization.

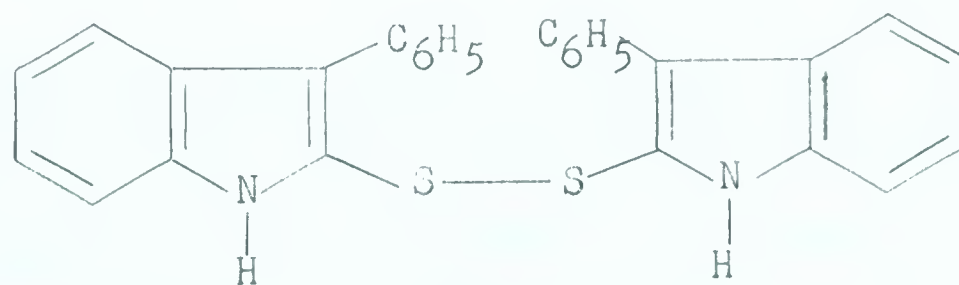
Both 3,3'-diindolyl disulphide, and 2,2'-dialkyl-3,3'-diindolyl disulphide have been prepared by Woodbridge

(80), by the treatment of indole or 2-alkylindole with iodine and thiourea in the presence of base. It is believed that a 3-iodoindole was first produced which then reacted with thiourea to form an isothiurea (LXVIII), which upon hydrolysis and oxidation gave the diindolyl disulphide.



LXVIII

Wieland et. al. (22) have described two synthetic sequences by which 2-alkylthio-3-phenylindoles may be prepared. The first method involved the reaction of sulphur dichloride on 3-phenylindole to yield the corresponding 2,2'-disulphide (LXIX), a



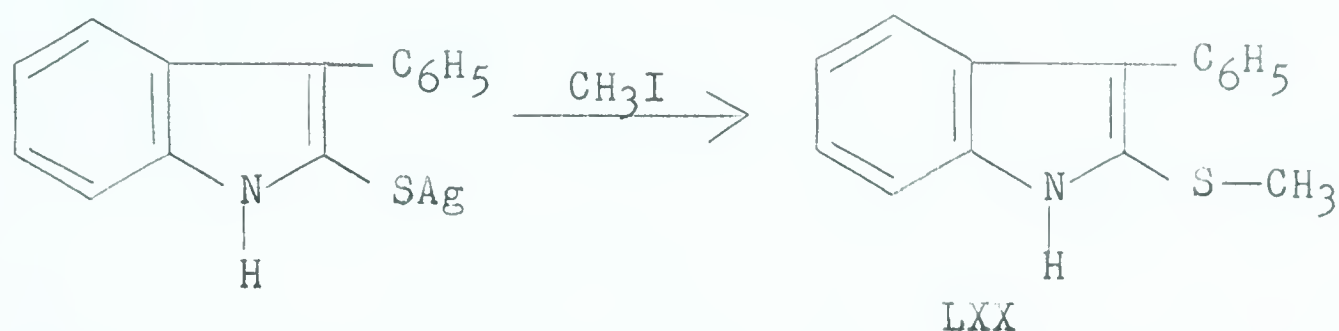
LXIX

reaction which was also applied to skatole, yielding similar results. The resulting disulphide could be reduced by zinc and



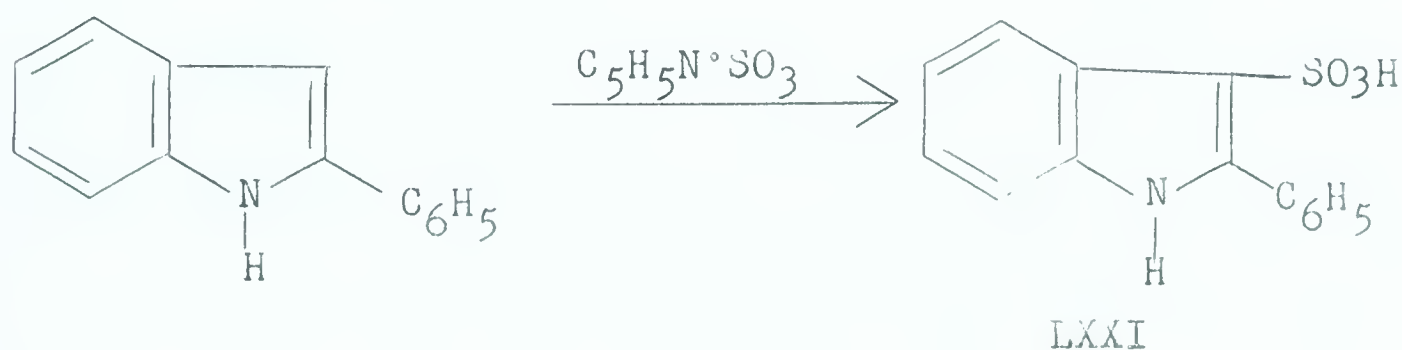


acetic acid to 2-mercapto-3-phenylindole. The silver salt of this mercaptan reacted with methyl iodide to yield 2-methylthio-



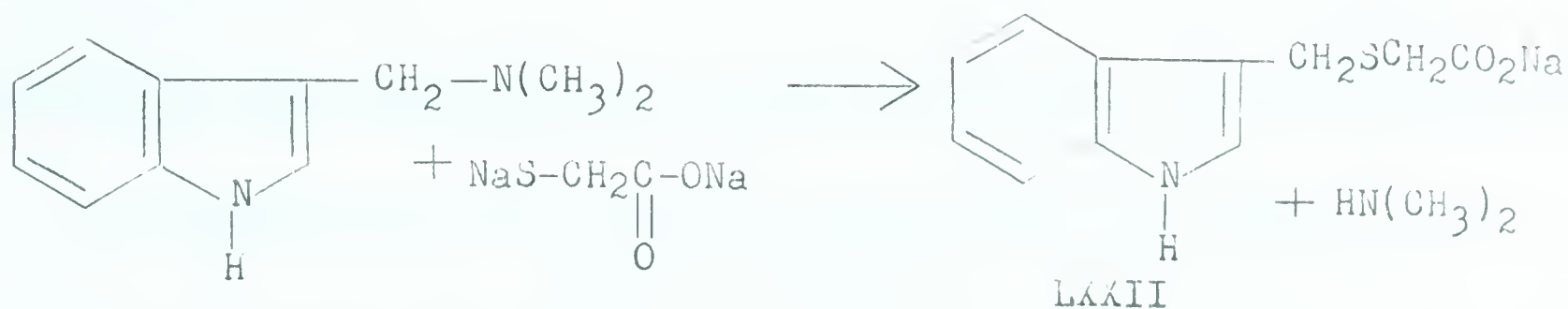
3-phenylindole (LXX). More simply, 3-phenylindole was shown to react with methane sulfenyl chloride, the product being 2-methylthio-3-phenylindole. Similarly, 2-mercaptoindole-3-acetic acid and its N-methyl homologue were prepared by the above sequences.

Several indole derivatives have been subjected to reaction with the pyridine-sulphur trioxide complex (81). Thus 2-phenylindole with the above complex yielded 2-phenylindole-3-sulphonic acid (LXXI). In a like manner, N-acetylindole and indole-3-acetic acid gave the corresponding 2-sulphonic acid derivatives.

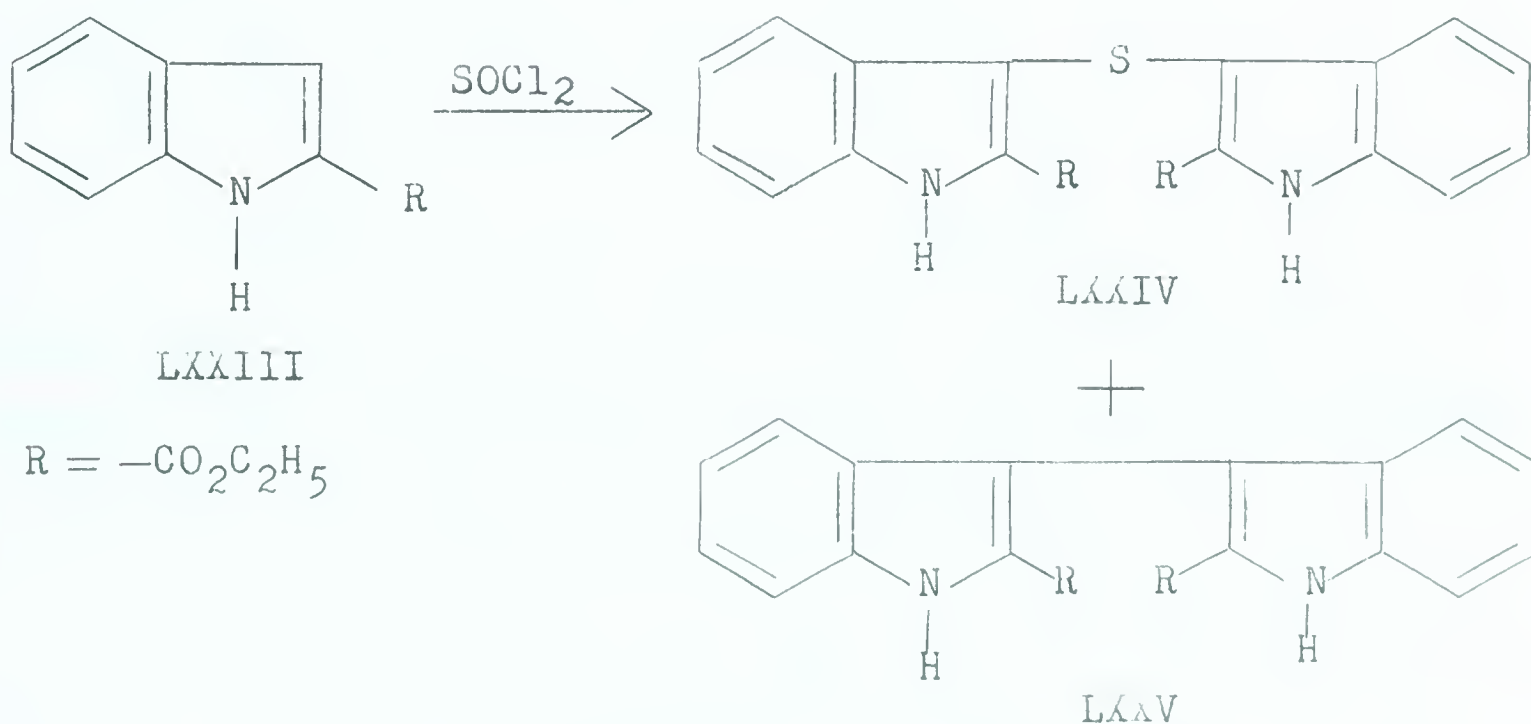


Gramine has been shown to undergo reaction with mercaptans in presence of base (82). For example, n-amyl mercaptan and sodium thioglycolate when treated with gramine produced respectively, 3-indolylmethyl n-amyl sulphide, and sodium 3-indolylmethylthioglycolate (LXXII). Similar reactions have been reported by Holt and Popplesdorf (83).





The reactions of ethyl indole-2-carboxylate (LXXIII) with thionyl chloride and sulphur dichloride, have been subjected to investigation (84). Thus ethyl indole-2-carboxylate reacted with thionyl chloride to produce bis-(2-ethoxycarbonyl-3-indolyl) sulphide (LXXIV), and bi (2-ethoxycarbonyl-3-indolyl) (LXXV).



To our knowledge, this is the extent of the recorded information on the methods of preparation of indolyl thioethers.

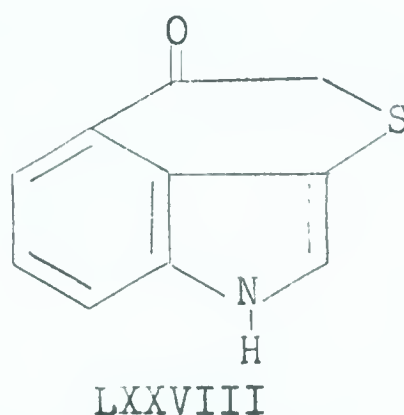
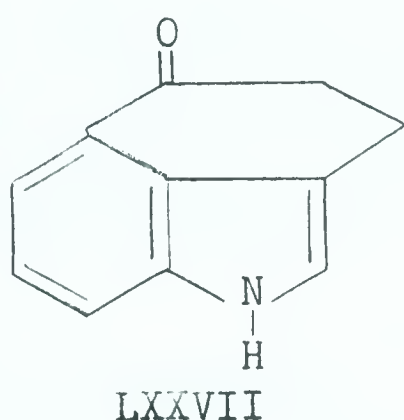


## RESULTS AND DISCUSSION

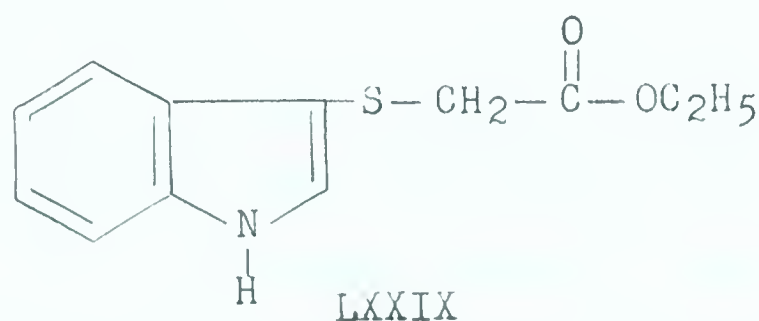
### 1. Williamson Ether Syntheses in Attempts to Produce 3-Alkylthioindoles.

#### A. The Reaction of N-Benzoyl-3-bromoindole with Ethyl Mercaptoacetate.

The success of Woodward et al (85) in the synthesis of d-lysergic acid from indole-3-propionic acid, prompted an attempt along similar lines. A key intermediate in Woodward's synthetic sequence is 5-keto-1,3,4,5-tetrahydrobenz-[c,d]-indole<sup>\*</sup>(LXXVII) obtainable from indole-3-propionic acid. It was hoped that the



synthesis of carbethoxymethylthioindoxyl (LXXIX) would provide a compound with the necessary structural features for conversion to (LXXVIII), the sulphur analogue of (LXXVII).



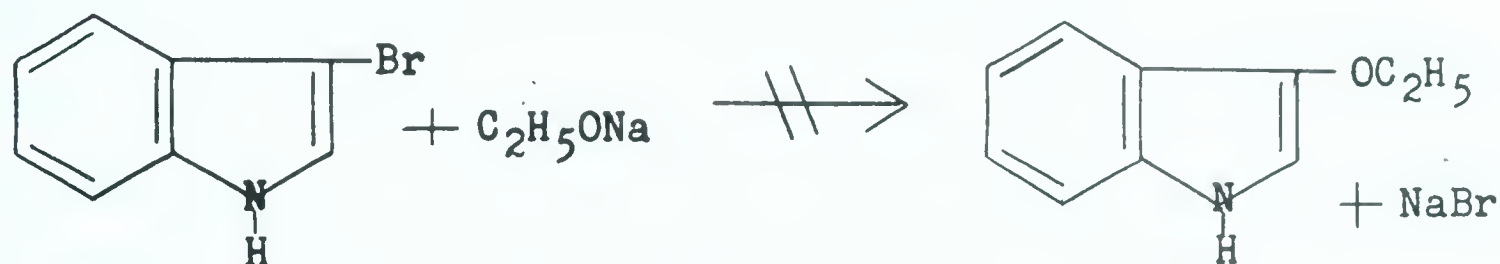
Some preliminary experiments, in which 3-bromoindole was treated with sodium ethoxide, showed that the ethoxide ion would

\* Woodward's nomenclature.

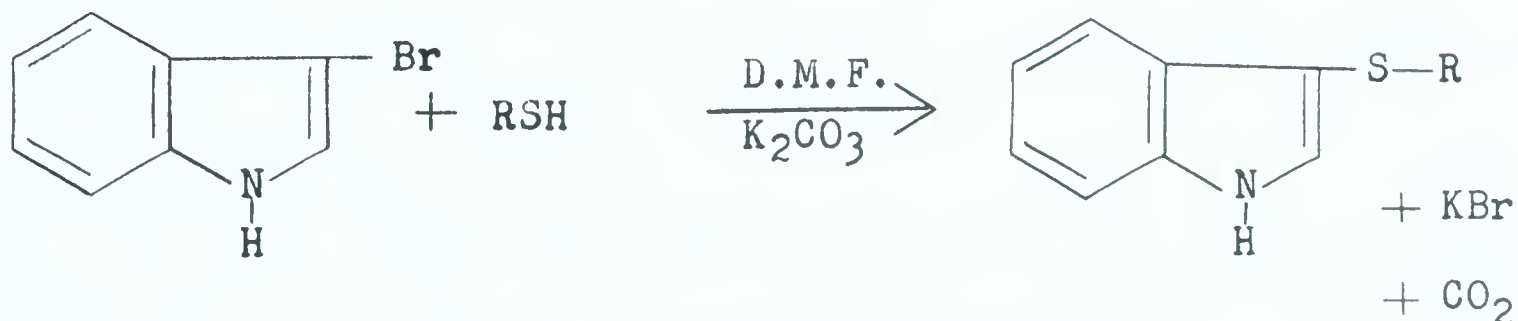




not displace the halogen in 3-bromoindole via a Williamson-type ether synthesis to give the expected 3-ethoxy-indole. However, the greater nucleophilicity of the alkali salts of mercaptans



(86) and the fact that Johnstone et al. (87) found the reaction of alkyl halides with 6-mercaptapurine to proceed readily in dimethylformamide containing potassium carbonate, led us to believe that similar reaction conditions might cause the anion of ethyl mercaptoacetate to displace the bromine atom of 3-bromoindole and produce the thioether (LXXIX).



(D.M.F. = dimethylformamide)

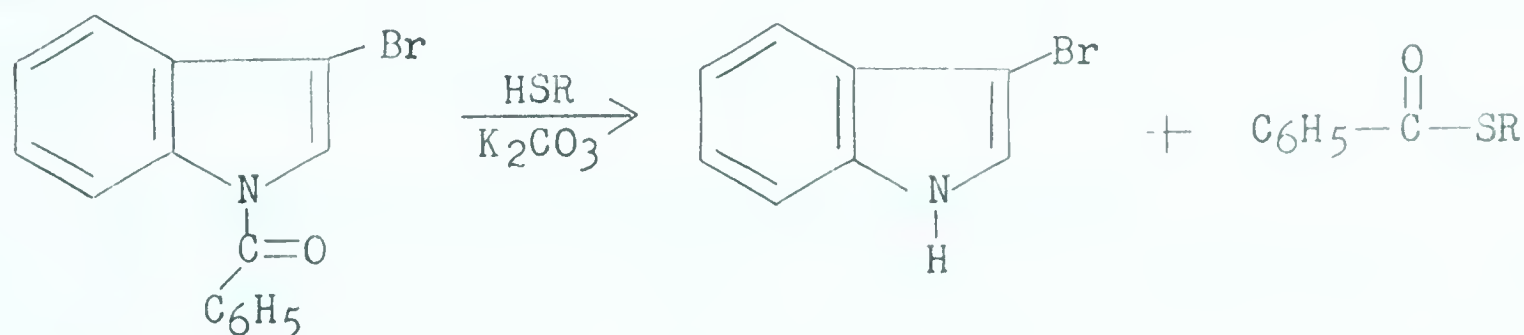
Some trial experiments showed that 3-bromoindole did not react with potassium ethyl mercaptide in dimethylformamide at  $60^\circ\text{C}$ ., nor did sodium ethyl mercaptide react with N-sodio-3-bromoindole. It was thought, however, that a benzoyl group attached to the pyrrole nitrogen of 3-bromoindole might improve the likelihood of displacement of the halogen by a nucleophilic species. This is in agreement with the prediction of a decrease



in electron density at the C<sub>3</sub> position as one proceeds from N-sodio-3-bromoindole to 3-bromoindole to N-benzoyl-3-bromoindole thus enhancing nucleophilic attack at this position.

Accordingly, equimolar portions of ethyl mercaptoacetate, N-benzoyl-3-bromoindole and potassium carbonate in dimethylformamide were kept at 60°C for two hours. Under these conditions, the occurrence of a reaction was clearly apparent. Concentration of an ether extract of the diluted reaction mixture, in an attempt to isolate and characterize products, resulted in a spontaneous exothermic decomposition, with production of hydrogen bromide and a dark greenish material. This behaviour, repeated in each attempt, posed a problem in the isolation of products. However it was later discovered that by reduction of the volume of ether at 0°C. with simultaneous addition of hexane, it was possible to avoid the decomposition, and thus isolate 3-bromoindole as one of the products of the reaction. It was the spontaneous decomposition of 3-bromoindole into the greenish material, which was responsible for the exothermic reaction.

It was apparent that a thioalcoholysis of the amide linkage had occurred as shown below. Additional evidence, besides the



formation of 3-bromoindole, that such a reaction had occurred was sought by attempted isolation of the compound  $\text{C}_6\text{H}_5-\text{C}(=\text{O})-\text{S}-\text{R}$





( $R = C_2H_5 - O - \overset{O}{\parallel} C - CH_2 -$ ). In order to do this, ether solutions, obtained from the reaction mixture which had undergone spontaneous decomposition due to the presence of the 3-bromoindole, were freed from the resulting greenish material by filtration. When the ether was removed, a yellowish oil was obtained, which gave a positive test for sulphur. Attempts to resolve this oil into pure compounds by distillation and crystallization failed. Schoberl and Whieler (96) had found that ethyl mercaptoacetate undergoes a series of self condensations under acidic conditions, leading to a mixture very difficult to resolve. It is quite possible that similar self condensation might have occurred under our conditions, accounting for the difficulties experienced in the isolation of pure products. In view of this, further work using ethyl mercaptoacetate, was discontinued in favour of simpler alkyl mercaptans.

#### Experiments Concerning the Decomposition of 3-Bromoindole.

Once it was known that the greenish material which was obtained during the attempted isolation of products from the reaction of N-benzoyl-3-bromoindole with ethyl mercaptoacetate was the result of decomposition of 3-bromoindole, this decomposition was given further attention.

##### 1. Improved Preparation of 3-Bromoindole.

In order to obtain adequate supplies of 3-bromoindole, some efforts were expended in seeking a simpler and more productive method for its preparation. The procedure of Weissgerber (63), employed at the present time for the synthesis of our 3-bromoindole,





gave a reasonably good yield (45%). However, the reaction path involving the conversion of indole to the N-sodic derivative which could be benzoylated and then halogenated, was time consuming. Accordingly other methods were investigated.

The few reports in the literature describing attempts at direct halogenation of indole in the pyrrole ring with bromine, chlorine or iodine (63, 92) indicate that a vigorous reaction does indeed occur. However, only in the case of iodination, and then only in dilute aqueous solution, has the isolation of a monohaloindole (3-iodoindole) been successful (68, 92). The reaction of chlorine and bromine with indole is reported to yield "a mixture of higher substitution products" (63) which apparently could not be resolved.

A more successful route to 3-bromoindole and 3-chloroindole was devised by Weissgerber (63) and is already cited above as the method employed in the present work. Other workers have reported that sulphuryl chloride converts indole into 3-chloroindole or 2,3-dichloroindole, depending upon the amount of halogenating agent used (65). In still another method, Buu-Hoi (93) found that the reaction of N-bromosuccinimide with N-benzoylindole gave a reasonably good yield of N-benzoyl-3-bromoindole which could be readily hydrolysed to 3-bromoindole (92).

The most recent and seemingly the simplest method is that reported by Yanovskaya (66) who stated that in dioxane solution at 0°C., the action of dioxane dibromide on indole gave a 60% yield of 3-bromoindole. This procedure in our hands, using purified dioxane solvent (94), gave only a very small amount of



material, which spontaneously decomposed on attempts at its purification, in the manner characteristic of 3-bromoindole. The temperature of the reaction solvent could not be reduced to 0°C., as reported, since the solvent solidified below 8°C. Hence we carried out the bromination at 8-10°C., but otherwise as described (66). The same procedure, modified by the addition of a small amount of diethyl ether as diluent for the dioxane to permit attainment of 0°C. reaction temperature gave the same "polymeric" material as before and little or no 3-bromoindole.

In the above reactions it was noted that hydrogen bromide evolved from the solution, especially near the end of the bromination reaction. Since Weissgerber found that 3-bromoindole decomposed readily when impure, or when in the presence of strong mineral acids, it was felt that some means of neutralizing or removing the acid would improve the reaction. The solvent pyridine proved to be the answer to the problem. When the halogenation was carried out using pyridine as solvent, indole could be converted into 3-bromoindole with dioxane dibromide in 48% yield. Use of pyridinium bromide perbromide as halogenating agent and pyridine as solvent, and carrying the reaction out at 0-2° C. increased the yield of pure 3-bromoindole to at least 64%. These latter improvements gave results that could be repeatedly obtained.

## 2. The Greenish Material Produced by Decomposition of 3-Bromoindole in Ether, Benzene or Hexane.

An ether solution of 3-bromoindole (63) was concentrated at 10°C.. A short-lived, vigorous reaction occurred, accompanied by





evolution of heat and hydrogen bromide and the appearance of the amorphous dark green material. In fact, as the reduction in volume of ether progressed, evidence of this reaction was noted at the sides of the container near the surface where solid 3-bromoindole formed. In all cases when the liquid had reached a sufficiently small volume so that 3-bromoindole appeared at the edges, reaction set in. The green material was separated by filtration, washed well with ether and dried. It melted over a range of 190-210°C. and gave a positive Ehrlich test for the indole nucleus with a free C<sub>2</sub> or C<sub>3</sub> position. It was insoluble in nonpolar or weakly polar solvents (benzene, ether, heptane) but quite soluble in highly polar organic solvents such as ethyl alcohol, dimethylsulphoxide and dimethylformamide. The substance showed no absorption (see Fig. 1, page 37) in the infrared region of 3300-3600 cm<sup>-1</sup> attributable to  $\text{>N-H}$  stretching characteristic of the  $\text{>N-H}$  group of indole, usually found at 3490 cm<sup>-1</sup> (88). Absorption did occur at 1582 cm<sup>-1</sup> attributed to  $\text{>C=N-}$  vibrations, which occur in the region 1590-1660 cm<sup>-1</sup> (89). These properties were also exhibited by the green material obtained from the reaction of N-benzoyl-3-bromoindole with ethyl mercaptoacetate.

In order to obtain, for comparison, a spectrum of a compound that is known to contain a  $\text{>C=N-}$  bond, the material 2,3,3-trimethylindolenine (LXXX) was prepared according to the method of Hoshino (90) by the reaction of 2,3-dimethylindole (95) with methylmagnesium iodide. The compound (LXXX), showed characteristic absorption for the  $\text{>C=N-}$  linkage at 1605 cm<sup>-1</sup>. The





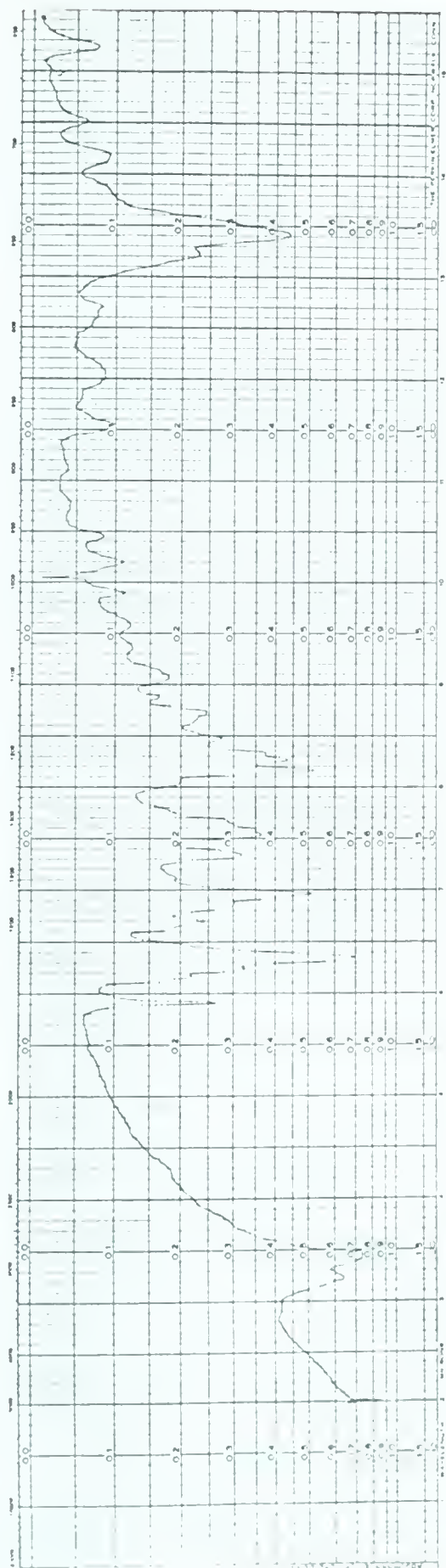


Fig. 1. I.R. Spectrum of the Decomposition Product of 3-Bromoindole.  
(Nujol mull).

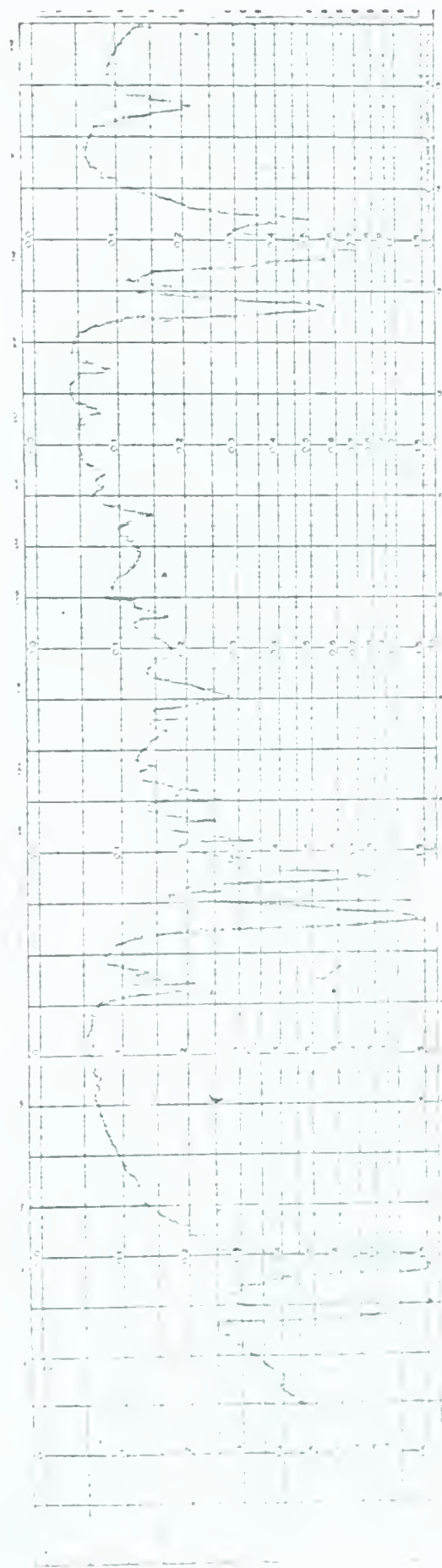
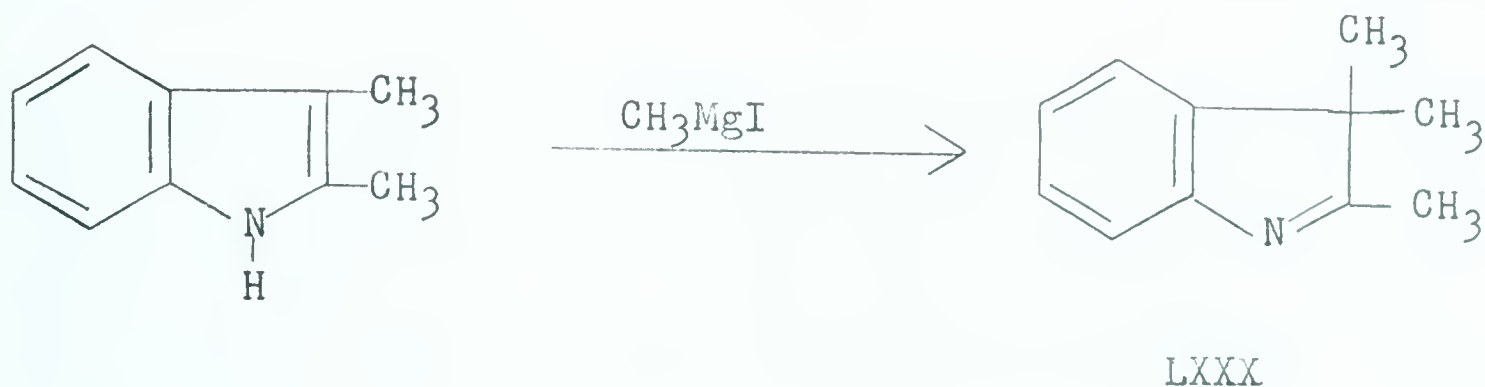


Fig. 3. I.R. Spectrum of "Solvated" Decomposition Product of 3-Bromoindole.  
(Nujol mull).





similarity of the spectral characteristics of 2,3,3-trimethyl-indolenine (LXXX) (Fig. 2, page 39) and of the decomposition product from 3-bromoindole suggested that the greenish material possessed an indolenine  $\text{>C=N-}$  grouping.

Attempts to purify the substance by crystallization from aqueous ethanol (20%  $\text{H}_2\text{O}$  by volume) gave a yellow solid which began to decompose at  $250^\circ\text{C}$ ., finally melting at  $285^\circ\text{C}$ . Infra-red analysis indicated strong  $\text{>N-H}$  stretching at  $3460\text{ cm}^{-1}$  (Fig. 3, page 37). This material also exhibited a positive Ehrlich reaction. Quantitative analysis of the thrice "recrystallized" material gave 64% C, 4.69% H, 8.64% N and 23.0% Br, which corresponds to an empirical formula of  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{Br}$  (roughly). Molecular weight determination by the Rast method gave a value of  $420 \pm 10\%$ . However due to the limited solubility of the substance in camphor, the figure 420 is not considered reliable.

The results indicate that 3-bromoindole undergoes polymerization with the elimination of some of the bromine as hydrogen bromide.

In view of the unsatisfactory results obtained in examination of the green material, and since elucidation of this material was not our aim, further work in this direction was discontinued.



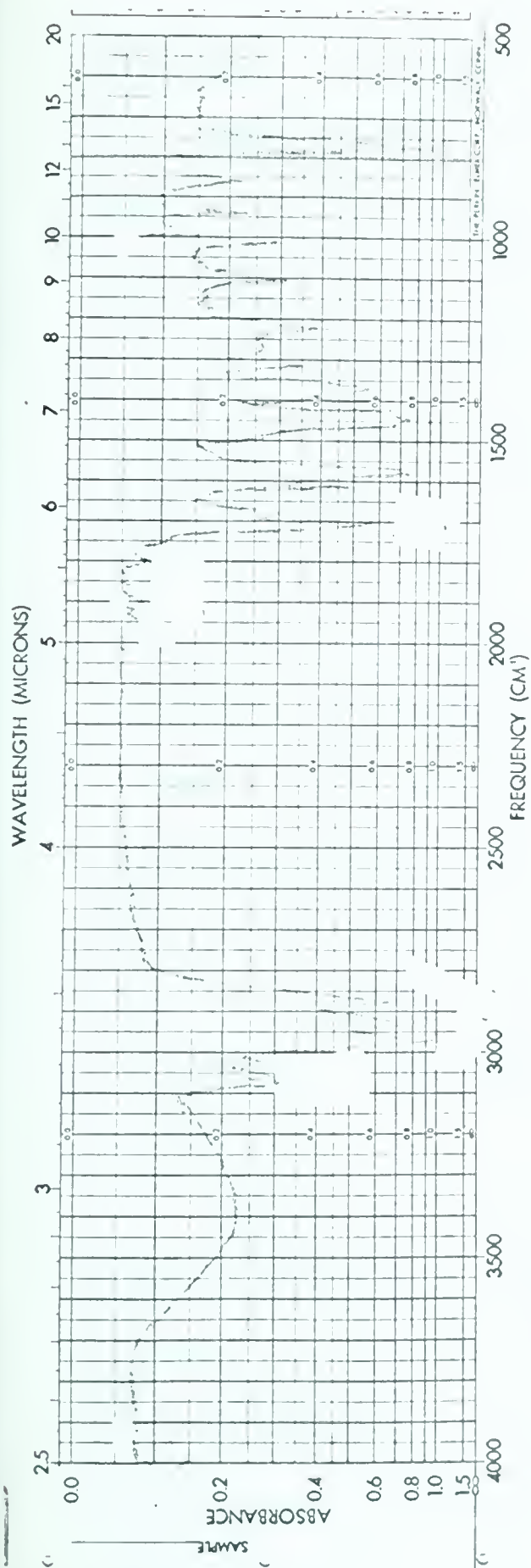


Fig. 2. I.R. Spectrum of 2,3,3-Trimethylindolenine.  
(Neat).

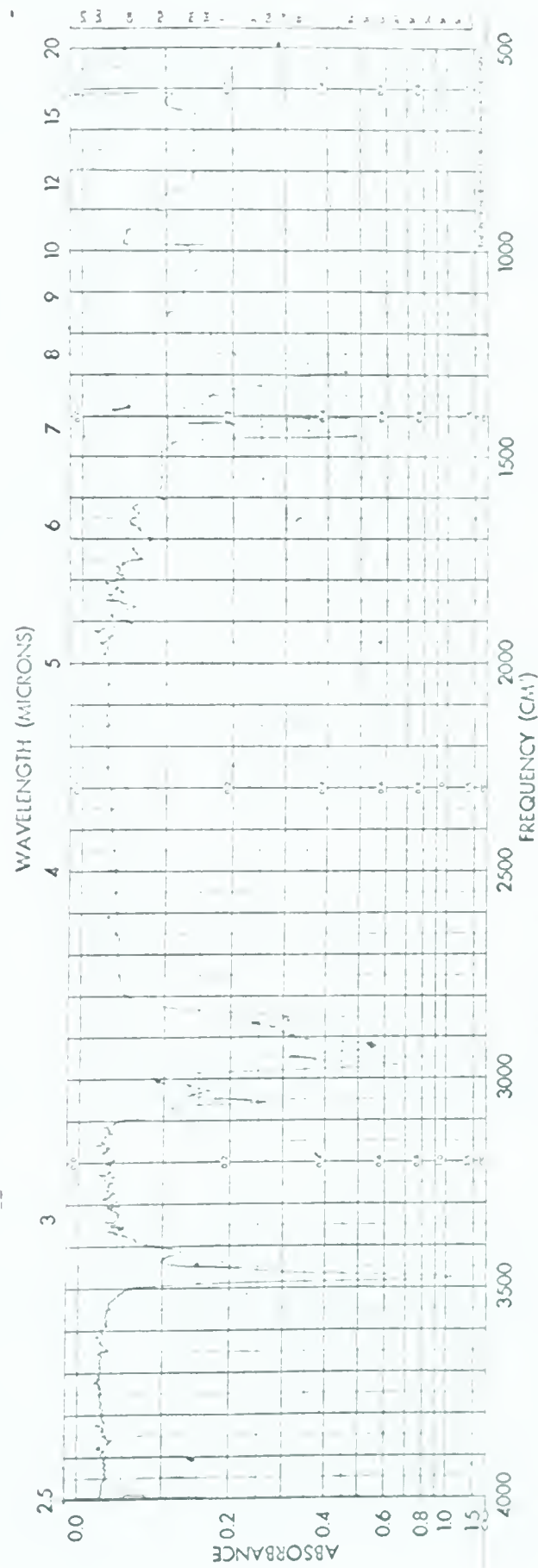


Fig. 4. I.R. Spectrum of 2-Ethylindole.  
(Solvent, CCl₄).







Indole Production During Decomposition of 3-Bromoindole in Ethanol or Dimethylformamide.

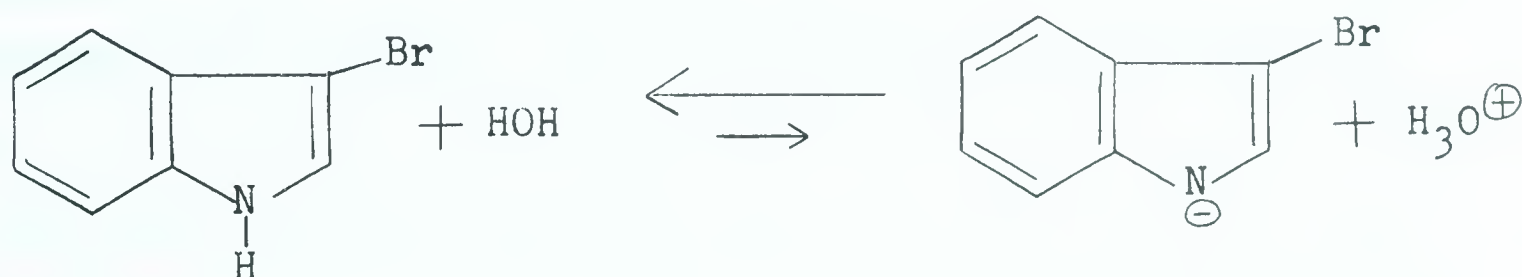
More useful information was obtained when 3-bromoindole was allowed to decompose in the solvents ethanol or dimethylformamide.

When 3-bromoindole was dissolved in ethanol containing sodium ethoxide and the solution refluxed for an extended time (24 hours) under nitrogen there was obtained a good yield (95%) of indole along with practically quantitative production of bromide ion. No 3-ethoxyindole was found, although it is possible that in fact 3-ethoxyindole may have been produced but underwent subsequent decomposition. The instability of 3-ethoxyindole has been reported (101) and we have found that even at  $-20^{\circ}\text{C}$ . under nitrogen, 3-ethoxyindole decomposes in a period of a few weeks. Ethanol (95%) itself was apparently sufficiently effective in bringing about reaction since refluxing an ethanolic solution of 3-bromoindole (12 hours) resulted in greater than 90% conversion to indole and bromide ion with no recovery of 3-bromoindole. In ethanol containing 20% water, essentially the same results occurred.

Indole was also obtained in good yield when 3-bromoindole and an equivalent amount of anhydrous potassium carbonate were heated in dry dimethylformamide (DMF) at  $150^{\circ}\text{C}$ . for twelve hours. No 3-bromoindole could be recovered. It is to be noted that a mixture of 3-bromoindole and anhydrous potassium carbonate, heated in DMF at  $60^{\circ}\text{C}$ . for 12 hours resulted in only 20% conversion. Increase in temperature accelerated the rate of decomposition into indole. Dimethylformamide itself, however, was ineffective



since a mixture of 3-bromoindole in this solvent, heated at 150°C. for 12 hours, produced no change in the indole. Apparently base is required in this solvent. Of further interest is the fact that when 3-bromoindole was refluxed for 12 hours in DMF containing water (10 ml. water/100 ml. DMF), approximately 30% of the 3-bromoindole was converted to indole and bromide ion, an observation which would lead one to suspect that the role of water was similar to that of ethyl alcohol above, probably functioning as a "base" in promoting the removal of a proton from 3-bromoindole, which could be the first step in the decomposition of that com-



pound. But there is to be considered the further observation that addition of water as well as potassium carbonate to DMF containing 3-bromoindole gave, after 12 hours of reflux, somewhat greater than 80% yield of indole. Approximately 5% of the 3-bromoindole was recovered. Apparently in this case water slowed down the decomposition relative to that found under anhydrous conditions where no 3-bromoindole remained.

In none of the cases above was there any evidence of the production of the greenish decomposition product that was found when either an hexane or ether solution of 3-bromoindole had been reduced in volume. As long as the 3-bromoindole was completely in solution, with none of it being formed at the edges of the





solution, this peculiar decomposition did not take place and one could reflux such solutions at temperatures as high as 150°C. (e.g. DMF) with no deleterious effect.

The analogue, 3-chloroindole (63) behaved in a similar manner, decomposing into indole and chloride ion when refluxed in ethanol containing sodium ethoxide or when heated in dry dimethylformamide containing anhydrous potassium carbonate.

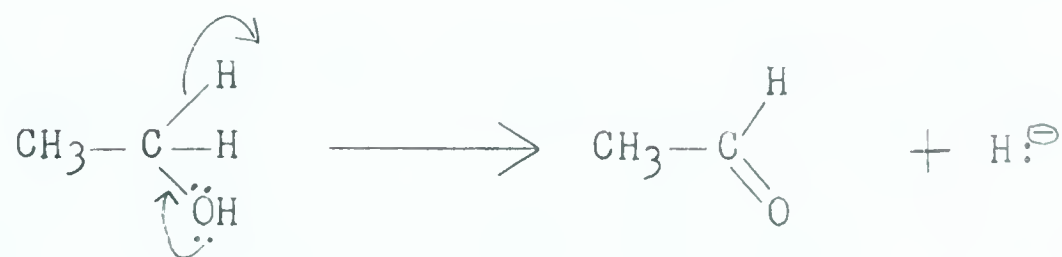
From the reactions described above it appears that a necessary feature for decomposition of 3-bromoindole is the presence of a base or proton acceptor. Since potassium carbonate was so effective in DMF, the same base was used in two other solvents, cyclohexene and dioxane. When 3-bromoindole was refluxed 12 hours, in dry dioxane (or cyclohexene) containing a suspension of anhydrous potassium carbonate no indole was formed, and the 3-bromoindole could be recovered in at least 85% yield. It was necessary to have a sufficiently large volume of solvent in these cases to ensure complete solubility of the 3-bromoindole thus avoiding the alternate decomposition mentioned previously. The failure to obtain any formation of indole may be due to the insolubility of potassium carbonate in these two solvents (a fact revealed by separate solubility tests).

The conversion of 3-bromoindole to indole and bromide ion in heated ethanol or in hot DMF containing water and/or potassium carbonate obviously is a reduction. The reduction must involve an oxidizable substance which can transfer electrons either as such or in the form of a hydride ion. Such a reduction can occur quite readily in the solvent ethanol which is readily oxidized to





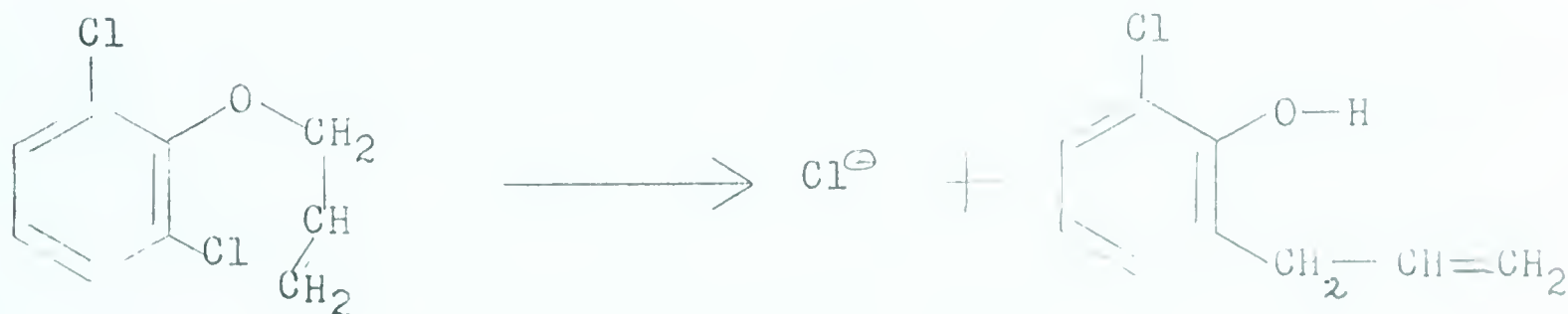
acetaldehyde or can donate a hydride ion during the reduction.



The smooth reduction of 3-bromoindole to indole and bromide ion by lithium aluminum hydride in refluxing tetrahydrofuran indicates that the hydride ion reduction process is conceivable.

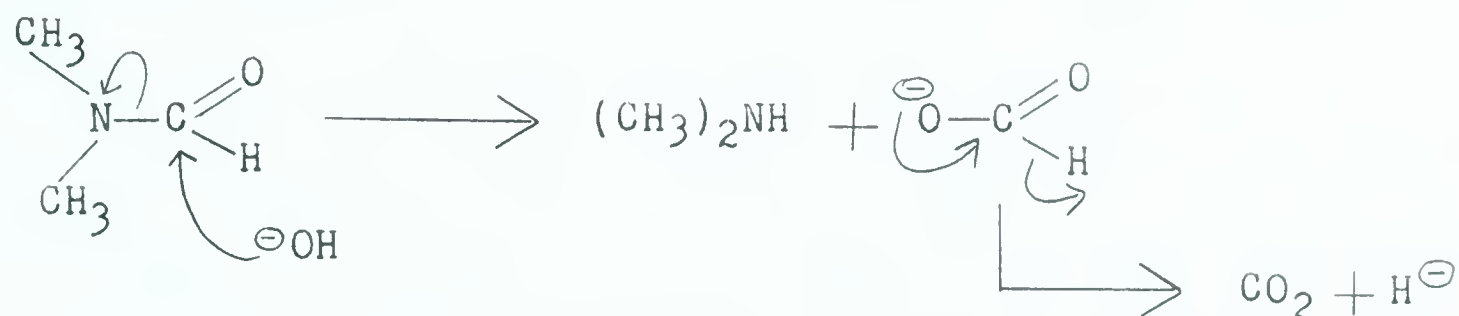
The formation of acetaldehyde is quite pronounced when ethanol is the solvent. It has been found that when 3-bromoindole is added to a definite quantity of 95% ethanol and the solution is refluxed under a stream of nitrogen, the odour of acetaldehyde is clearly perceived in the effluent gases.

The source of electrons or hydride ion in DMF could conceivably come from the DMF itself since DMF can be oxidized. In another problem investigated in this laboratory it has been shown that with DMF as solvent, a great deal of reductive elimination of halogen occurs in the Claisen rearrangement of allyl 2,6-dihalophenyl ether (91). Such reductive elimination practically disappears when solvents which are not easily oxidized are used.



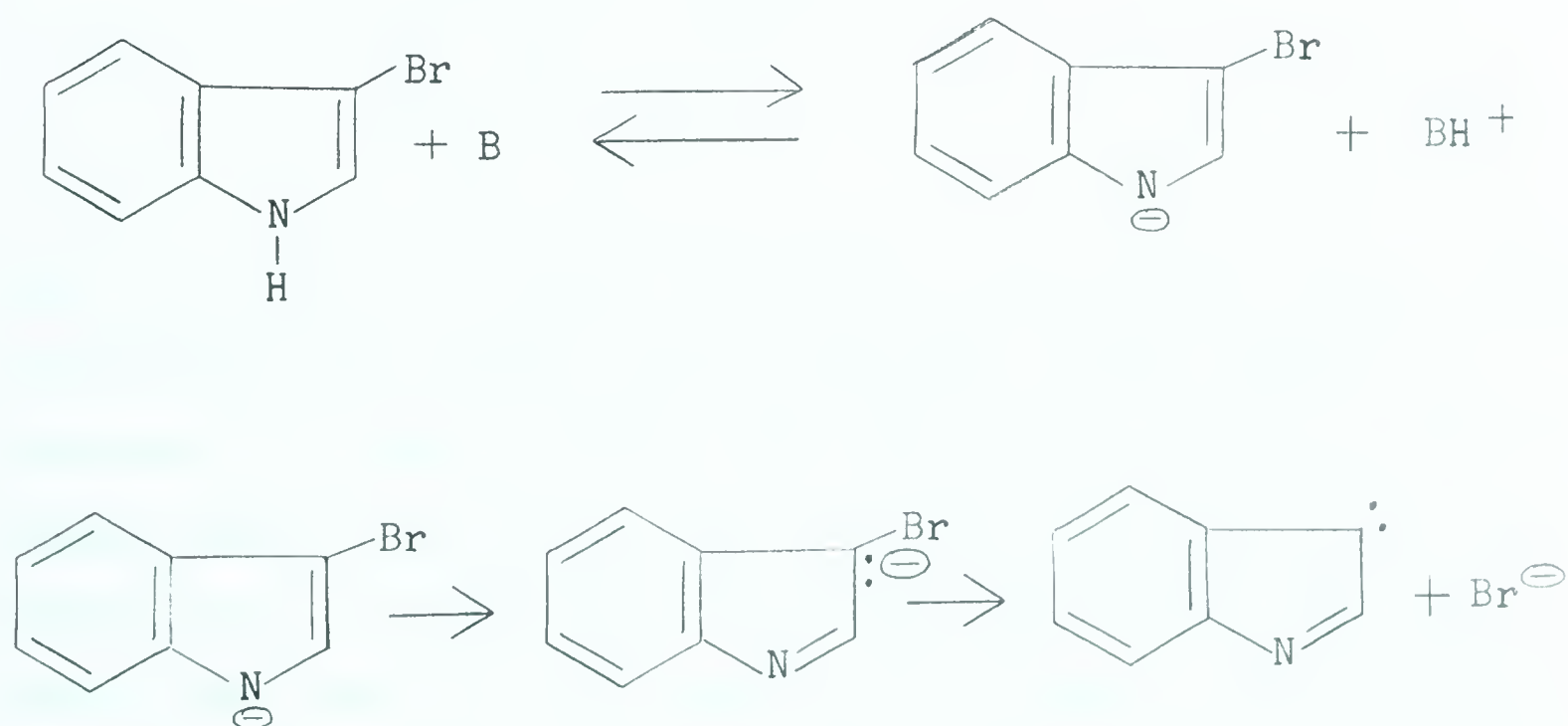


The possibility that a hydride ion transfer takes place via the route

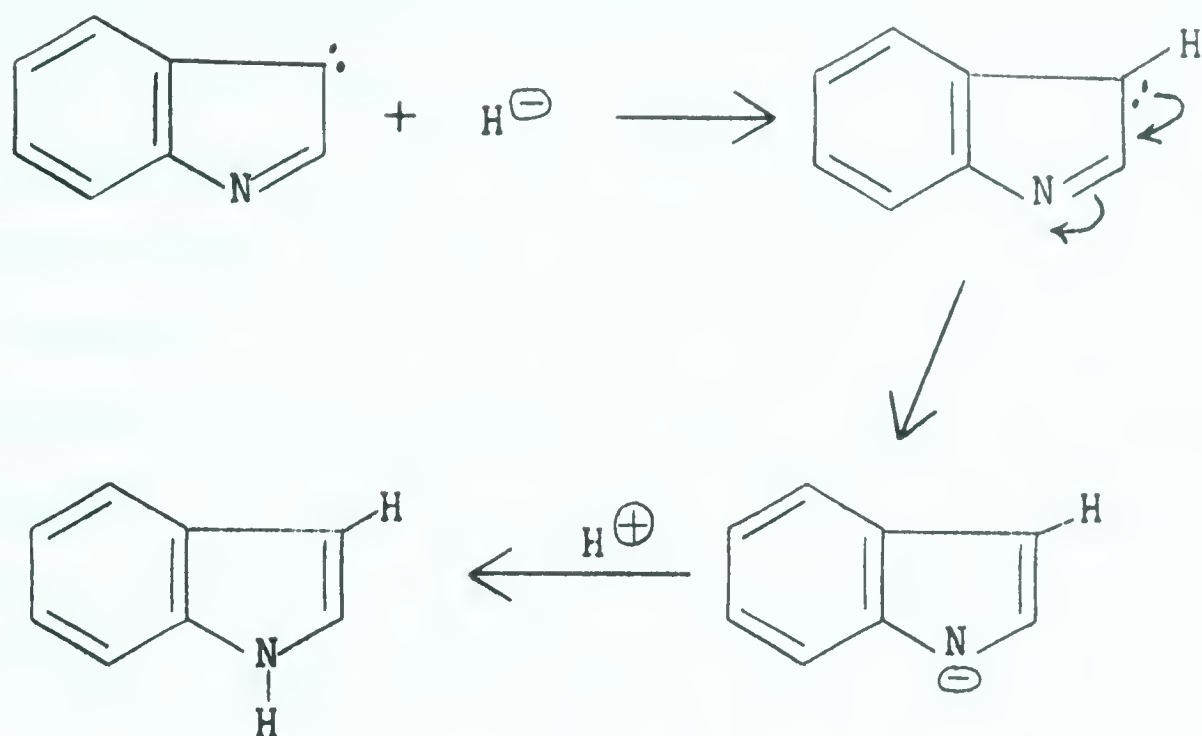


is supported by the detection of dimethylamine as one of the products of the effluent gas carried by the nitrogen stream both by its odor and by the precipitation of dimethylamine hydrochloride from the ether used as collecting trap.

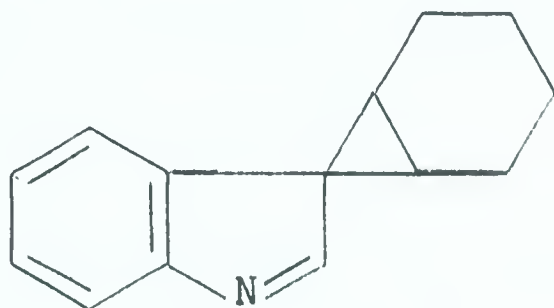
There is the possibility that the decomposition of 3-bromo-indole goes via a carbene involving a base as shown below.







In an attempt to provide some evidence for this viewpoint, a mixture of 3-bromoindole and phenyl lithium was heated in refluxing cyclohexene with the hope that the carbene adduct



would be obtained. However the reaction was quite complex, giving a very dark tarry product which contained a small amount of indole and at least 12 other indole derivatives (giving positive Ehrlich tests) as shown by thin layer chromatography along with material which is insoluble in benzene. No further work was done on this reaction thus leaving the problem of the decomposition of 3-bromoindole still unsettled. Our main interest in this reaction was that it supplied an explanation for the formation of indole in some of the reactions involving 3-bromoindole described in the following portions of the thesis.





B. Reaction of N-Benzoyl-3-bromoindole with Simple Alkyl Mercaptans.

The reaction between N-benzoyl-3-bromoindole and a mercaptan in the presence of  $K_2CO_3$ , was repeated but this time with ethyl mercaptan rather than ethyl mercaptoacetate. The same spontaneous decomposition of the 3-bromoindole in the ether extract of the diluted reaction mixture occurred, when the volume of ether was reduced, yielding the greenish material described in the preceeding section. Changing to the solvents dioxan or tetrahydrofuran or using n-propyl mercaptan or n-amyl mercaptan in dimethylformamide, or varying the reaction time between 0.5 hours to 12 hours gave similar results to those obtained above.

Since the examination of the decomposition of 3-bromoindole had revealed that in dimethylformamide the 3-bromoindole in the presence of  $K_2CO_3$  was converted into indole and bromide ion in a period of 12 hours, when the reaction temperature was  $150^\circ C.$ , these conditions were thought to be more suitable to avoid the problem of the spontaneous decomposition of 3-bromoindole which might occur in the process of isolation of products. Accordingly the reaction between equimolar amounts of N-benzoyl-3-bromoindole, ethyl mercaptan and anhydrous potassium carbonate in dimethylformamide at  $150^\circ C.$ , was examined. Such a mixture was heated for 12 hours, cooled, diluted with water and ether extracted. The ether extract was washed with aqueous silver nitrate, to remove unreacted mercaptan, then with water and finally dried. Removal of the ether under reduced pressure and fractional distillation in vacuo yielded ethyl thiolo benzoate (48% based on



N-Benzoyl-3-bromoindole), indole (28.4%), and 3-ethylindole (24.5%). The distillation was accompanied by considerable decomposition, resulting in much tarry material in the residue. Neither 3-bromoindole nor 3-ethylthioindole were obtained. However later work in which 3-ethylthioindole was prepared by another route, showed that much decomposition accompanies the distillation of 3-ethylthioindole. This fact, along with the knowledge that 3-bromoindole also decomposes when heated, might account for failure to obtain these two substances.

In a second and similar experiment, the ether extract was reduced in volume and aliquots analysed by G.L.C. on Apiezon "L"\* (20% on Kromat F.B. 30-60 mesh) using helium as carrier gas. A number of peaks appeared on the chromatogram, several of which were identified as being due respectively to diethyldisulphide, indole, 3-ethylindole and ethyl thioloobenzoate. There were at least four other peaks present, one of which was identical in retention time to that of authentic 3-ethylthioindole (prepared later). The fact that 3-bromoindole is sensitive to heat prevents passage unchanged through the G.L.C. column.

In another experiment carried out at 60°C. for 2 hours the ether extract was reduced in volume with simultaneous exchange of ether for benzene, and the resulting solution chromatographed on neutral alumina (activity grade 1). Elution with pentane resulted first in the separation of indole, followed by 3-bromoindole. The remaining fractions were oils, from which no crystalline material could be obtained. However fractions collected using benzene as eluent gave a reaction with mercuric chloride in

\*Similar results were also obtained on Silicon Rubber (20% on Kromat F.B. 30-60 mesh).



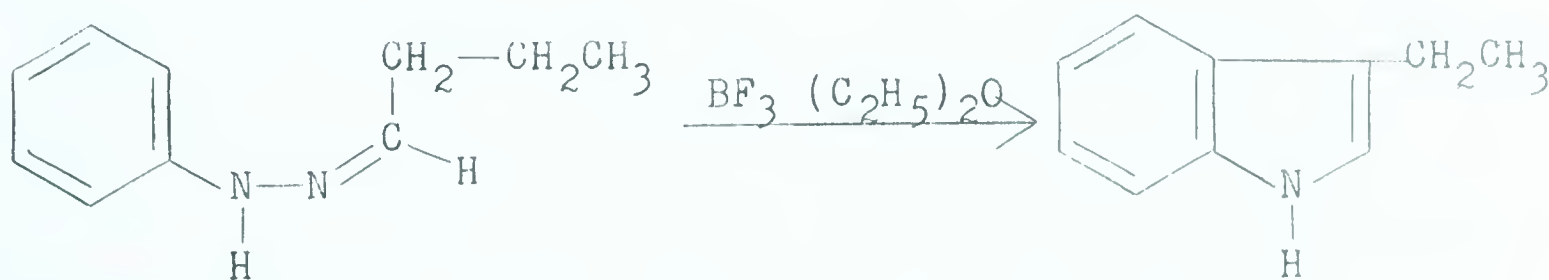


ethanol, producing ethylthiomercuric chloride ( $C_2H_5-S \ Hg-Cl$ ) (98), indicative of an unsymmetrical thioether, possibly 3-ethylthioindole.

Identification of the products was made by comparison of the infrared spectra with those of authentic compounds, and by melting point and mixed melting point and by picrate formation.

The formation of diethyl disulphide is readily understood since exposure of ethyl mercaptan to air or other oxidizing media is known to produce diethyl disulphide (99).

That the alkyl indole produced was really 3-ethylindole and not 2-ethylindole was proven by preparation of authentic samples of both of these substances. The 2-ethylindole was obtained by the method of Verley and Beduwé (103) from o-propionotoluidide. The picrate of 2-ethylindole melted at  $123^\circ C$ . as reported in the literature (103). The modified method of Korizynski (105) was used to synthesize authentic 3-ethylindole by a boron trifluoride catalysed cyclization of n-butyraldehyde phenylhydrazone. The picrate of 3-ethylindole melted at  $143^\circ C$ .



The ethylindole obtained from the reaction of N-benzoyl-3-bromoindole with ethyl mercaptan in the presence of potassium carbonate gave a picrate melting at  $143^\circ C$ ., which on admixture with the picrate of authentic 3-ethylindole showed no depression.





A mixture of the picrates of 2-ethylindole and the alkyindole from our reaction did give a depression. The infrared spectra of our alkyindole was identical with that of authentic 3-ethylindole but not with that of authentic 2-ethylindole (Fig. 4, page 39; Figs. 5 and 6, page 50). Both 2-ethylindole and 3-ethylindole melted at 43°C. (102, 103). Because of the low melting points and the resulting greater difficulties in crystallization of these ethyl indoles, the picrates were preferred as the means of identifying the 3-ethylindole.

The formation of 3-ethylindole in this reaction is not clear. Indole has been alkylated with ethanol under acidic or basic conditions at 180-200°C. (106). However no alkylation of indole by ethyl mercaptan was found when indole, ethyl mercaptan and potassium carbonate were heated in dimethylformamide at 150°C. for 6 hours, the conditions used in our reaction. Furthermore, ethyl thioloibenzoate did not interact with indole or 3-bromoindole, when these reagents were distilled together, to produce 3-ethylindole. In the case of 3-bromoindole only, the usual decomposition of the indole was observed.

Ethyl thioloibenzoate was identified by comparison of its infrared spectra, G.L.C. retention time, and boiling point with those of an authentic sample (107). Ethyl thioloibenzoate obviously occurs via facile attack of the ethyl mercaptide ion on the amide linkage producing the anion of 3-bromoindole. This anion at the lower temperatures of reaction or at reaction times of less than 4-6 hours obtains a proton to form 3-bromoindole. This anion also decomposes into indole and bromide ion, both of



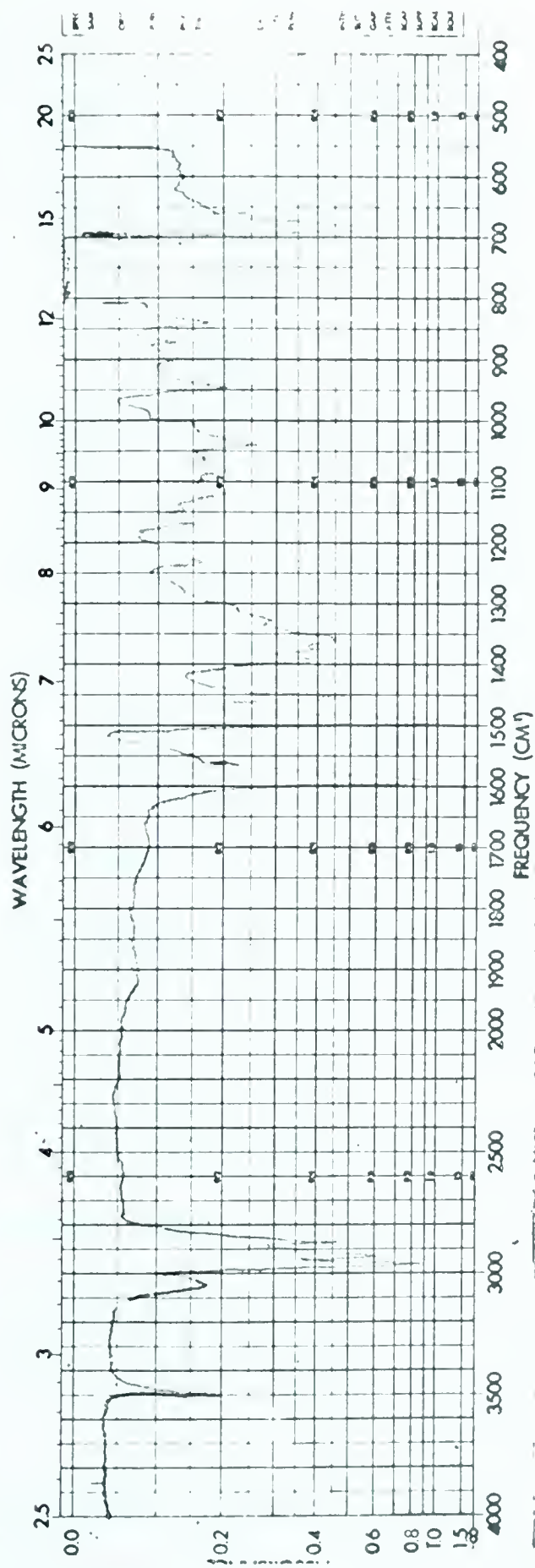


Fig. 5. I.R. Spectrum of 3-Ethylindole.

(Solvent,  $\text{CCl}_4$ ).

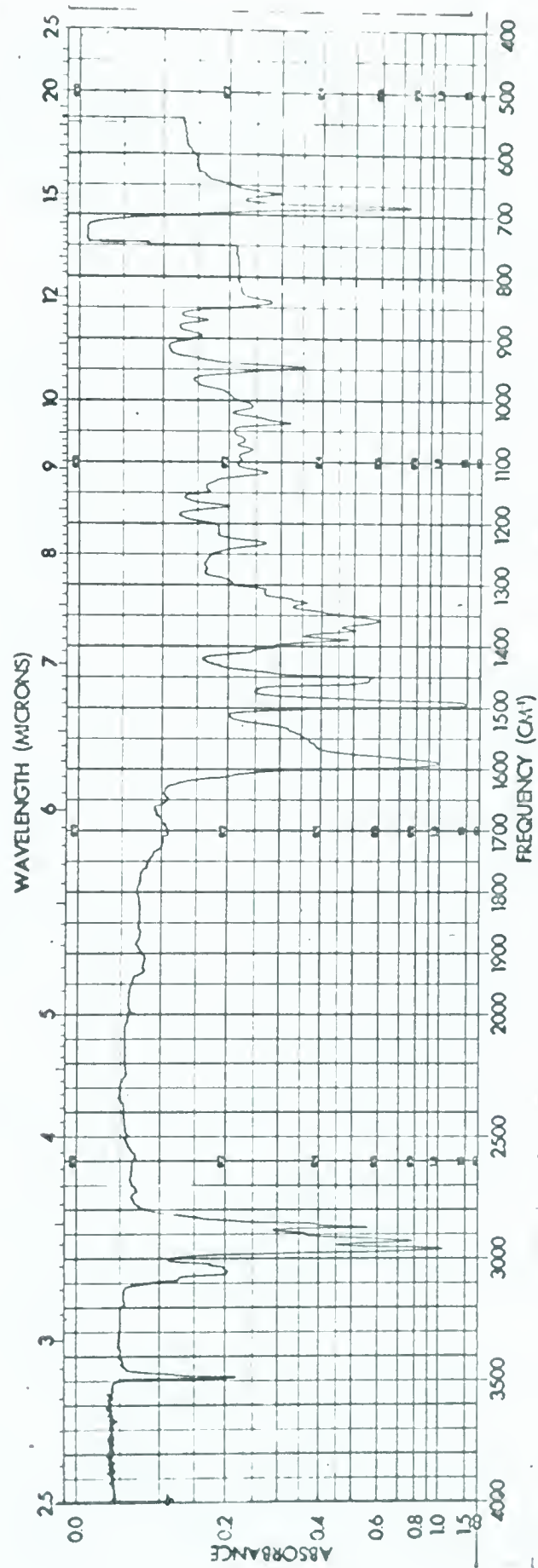
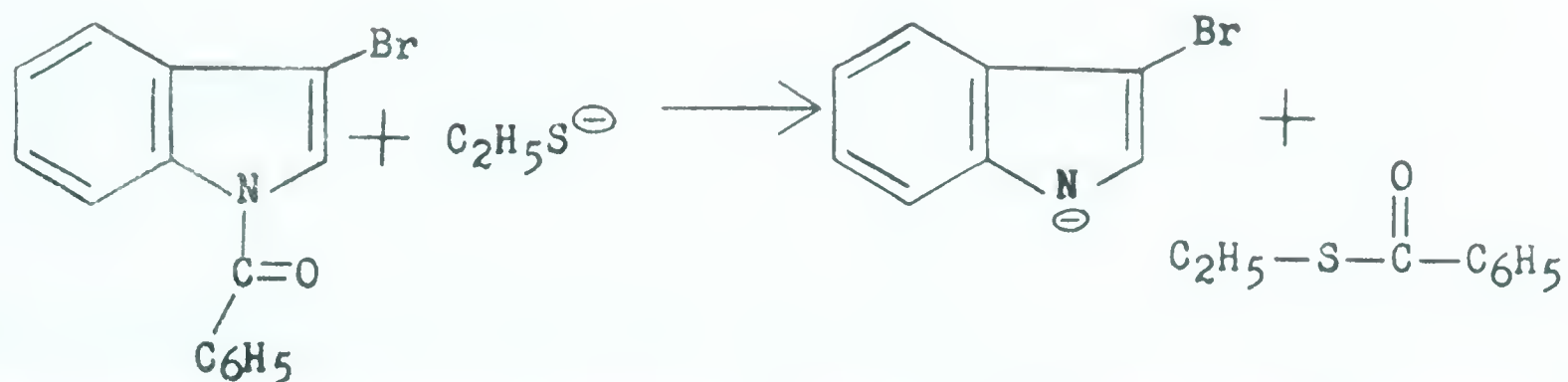


Fig. 6. I.R. Spectrum of Suspected 3-Ethylindole.

(Solvent,  $\text{CCl}_4$ ).







which are found in the reaction mixture. Undecomposed 3-bromoindole was obtained only when isolation procedures avoided excessive heat and rapid evaporation of solvent leading to deposits of solid 3-bromoindole, which then would decompose.

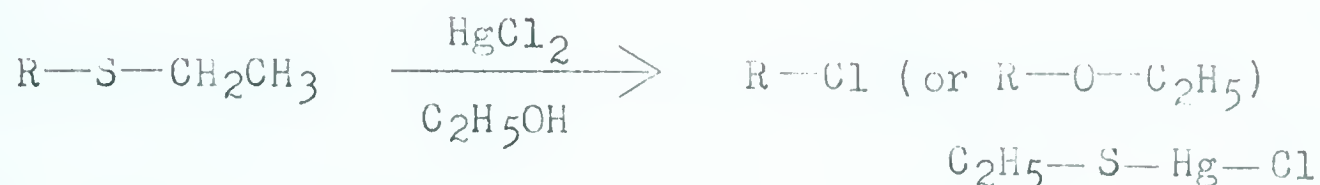
That the attack of ethyl mercaptide occurs mainly, if not exclusively at the amide linkage is supported by the large amount of ethyl thiobenzoate produced (48%) and by the fact that in one method of preparation of 3-bromoindole, N-benzoyl-3-bromoindole is treated with aqueous alcoholic base (63) to hydrolyse the amide linkage. However direct attack of the ethyl mercaptide ion at C<sub>3</sub> with elimination of bromide ion is not ruled out as a competing reaction. We have not been able to isolate N-benzoyl-3-ethylthioindole, but this may be due to rapid debenzoylation of this molecule by ethyl mercaptide ion.

The fraction obtained from the experiment in which the ether extract had been resolved on neutral alumina, using benzene as eluant, was suspected as being largely 3-ethylthioindole, because it gave not only a positive Ehrlich test but also a characteristic reaction with an ethanolic solution of mercuric chloride. This reaction gave a readily isolatable precipitate of ethylthiomer-





curic chloride, and is shown below.



The identification of ethylthiomercurichloride was made by comparison of its infrared spectrum and of its x-ray scatter patterns, with those of an authentic specimen made by the method of Challenger and Rawlings (98) (Fig. 7, page 53).

The same precipitate of ethylthiomercuric chloride was obtained when an ether solution of the products obtained from the reaction of N-benzoyl-3-bromindole, ethyl mercaptan and potassium carbonate in dimethylformamide, first freed from unreacted ethylmercaptan by several washings with aqueous silver nitrate, was treated with an alcoholic solution of mercuric chloride.

In separate tests, ethylthiolobenzoate and diethyldisulphide, other products of the reaction of ethyl mercaptan with N-benzoyl-3-bromoindole, were shown to be inactive towards ethanolic mercuric chloride, failing to give ethylthiomercuric chloride under the usual reaction conditions. On the other hand ethyl mercaptan did react with mercuric chloride, hence it was necessary to remove this mercaptan as the insoluble silver salt by washing the ether extract of the mixture with aqueous silver nitrate, prior to testing the ether solution or products from it for the ethyl thioether group.

In several cases, thioethers have been isolated as a complex



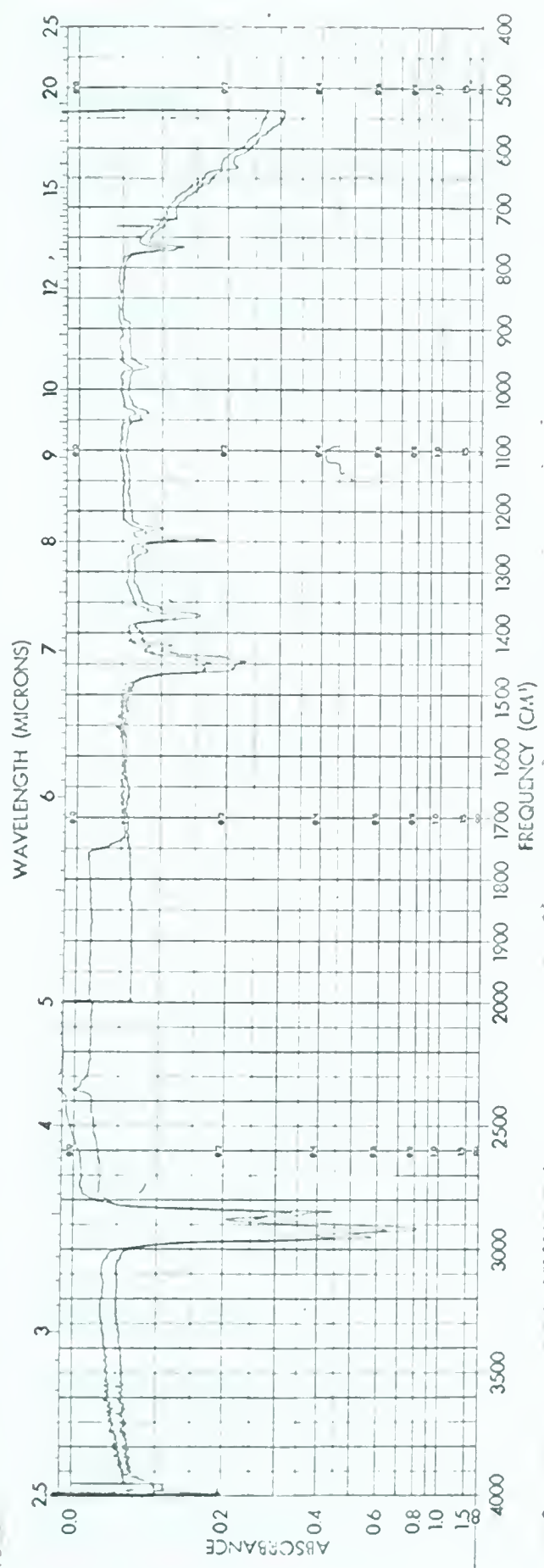


Fig. 7. Comparative I. R. Spectrum of Ethylthiomercuric Chloride.  
(Nujol mull).

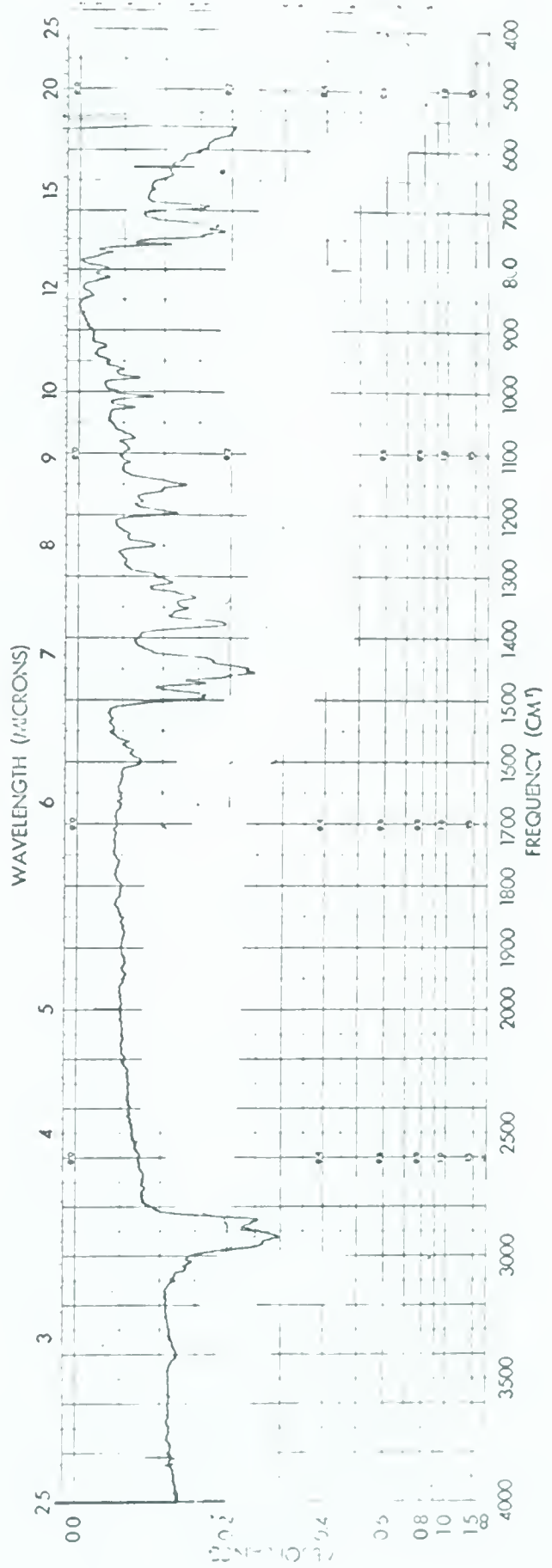
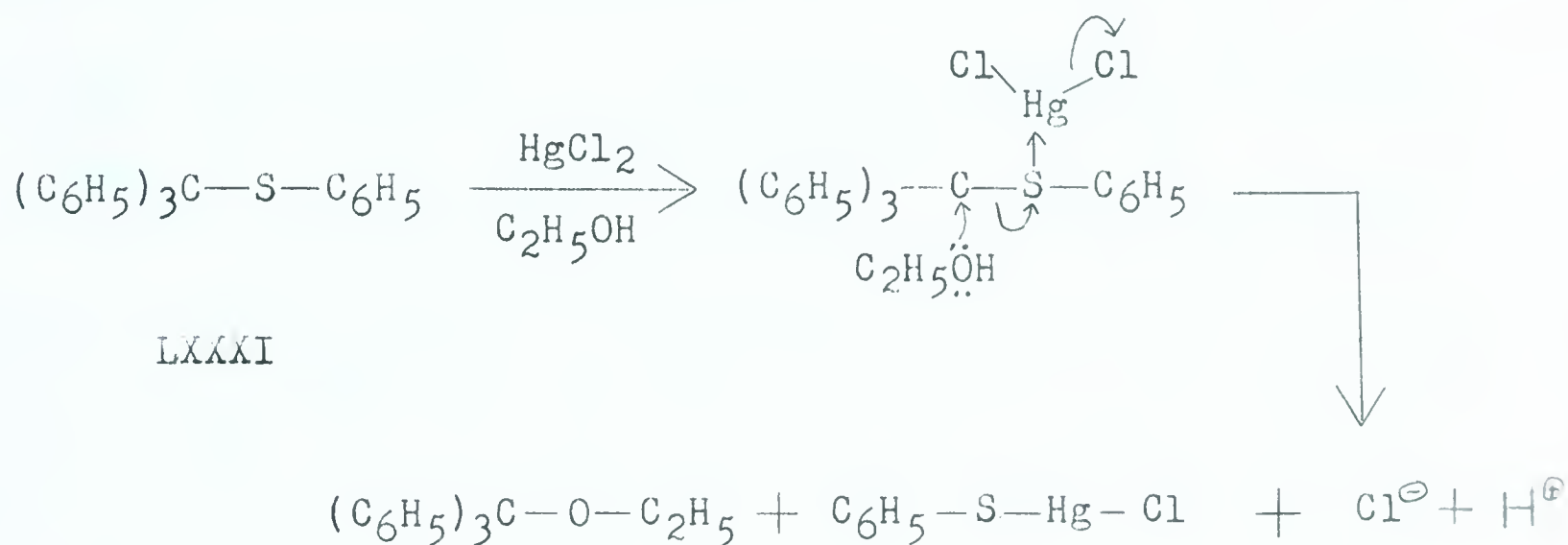


Fig. 8. I.R. Spectrum of N,N'-Dibenzyl-3,3'-diindolyl Disulphide.  
(Nujol mull).



with a heavy metal metal salt (97). Gregg, Iddles and Searns (100) found that some unsymmetrical thioethers were cleaved when treated with mercuric chloride. Two instances cited were the cleavage of triphenylmethyl phenyl sulphide (LXXXI) and triphenylmethyl o-tolyl sulphide. In each instance, the thioether cleaved in such a way that the group least able to form a carbonium ion attached itself through the sulphur atom to mercury. The remaining carbonium ion was then attacked by solvent.

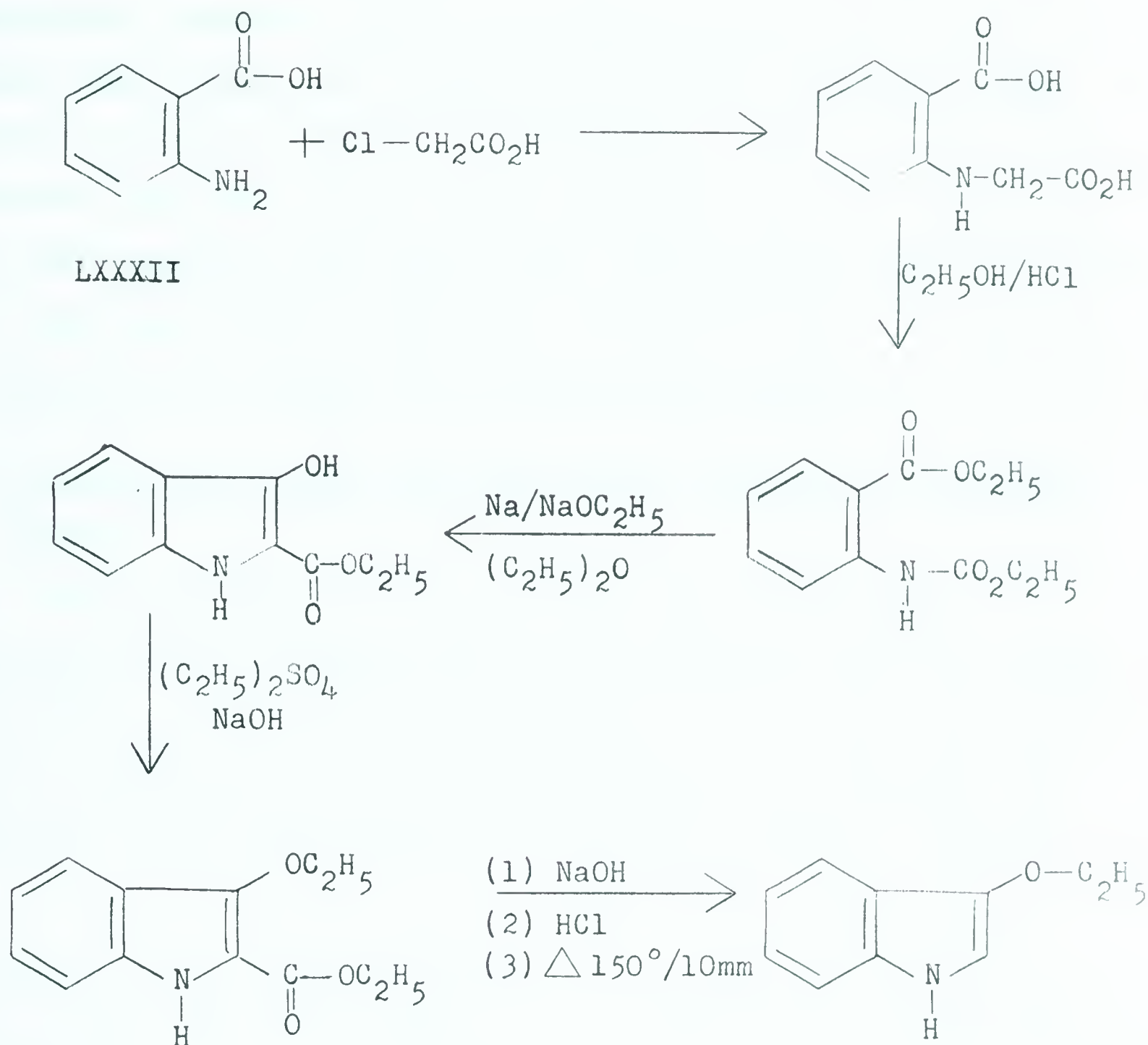


We have found that authentic 3-ethylthioindole, prepared by a route described later, did react with alcoholic mercuric chloride yielding ethylthiomercuric chloride, indole and 3-ethoxyindole. The ethylthiomercuric chloride was obtained in nearly quantitative yields, while only traces of indole and 3-ethoxyindole were indicated. The indole and 3-ethoxyindole were detected by thin layer chromatography, using authentic indole and 3-ethoxyindole for comparison. The chromatograms were developed using Ehrlich's reagent (71). A sample of 3-ethoxyindole was prepared by a modification of the methods employed by A. Etienne (101) and A. Baeyer (102) from anthanilic acid (LXXXII) and





chloroacetic acid by the sequence shown below.



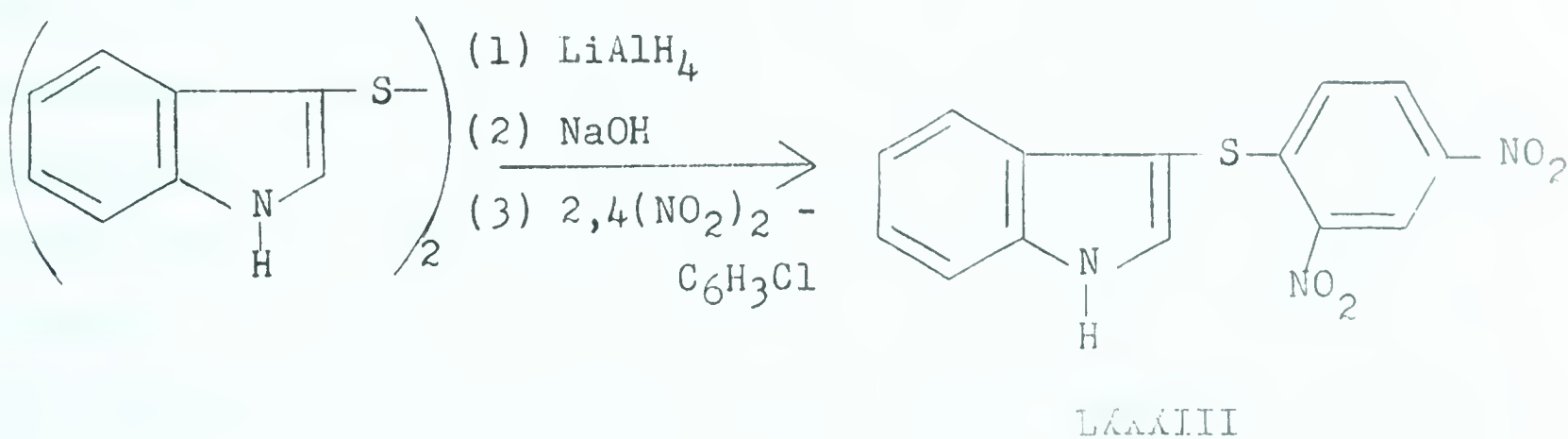
It is quite apparent from the foregoing work that the use of N-benzoyl-3-bromoindole with mercaptans in the presence of potassium carbonate is quite complex resulting in only a small amount of 3-ethylthioindole. Furthermore isolation of this C<sub>3</sub> thio compound is difficult. Accordingly this method was discarded as a means of obtaining the 3-indolylthioether linkage. However, some of the aspects of the reaction are extremely interesting and warrant further investigation.



Although the reaction of N-benzoyl-3-bromoindole with mercaptans produced interesting features which required further work, such efforts were abandoned due to the persistent generation of allergic reaction in the worker. Whenever these reactions were carried out and product analysis made, mild to serious allergic symptoms were experienced. They required medical attention and antihistamine injections. For this reason work was discontinued with a number of questions left unanswered.

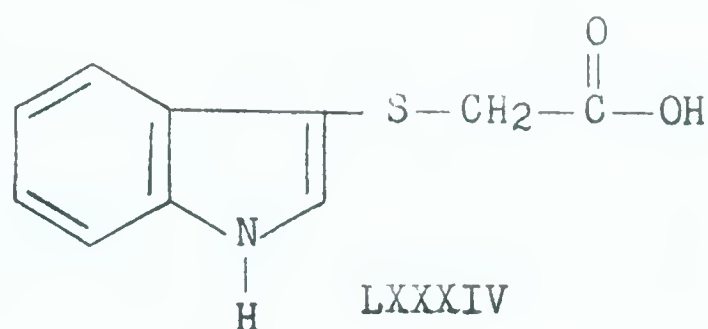
C. The Reaction Between Reduced Diindolyl Disulphide and Benzyl Iodide.

Grant and Snyder (76) have shown that 3,3'-diindolyl disulphide can be reduced with lithium aluminum hydride in tetrahydrofuran. They treated the reduction product with sodium hydroxide followed by 2,4-dinitrochlorobenzene, and obtained a 37% yield of 3-(2,4-dinitrophenylthio)-indole (LXXXIII). However

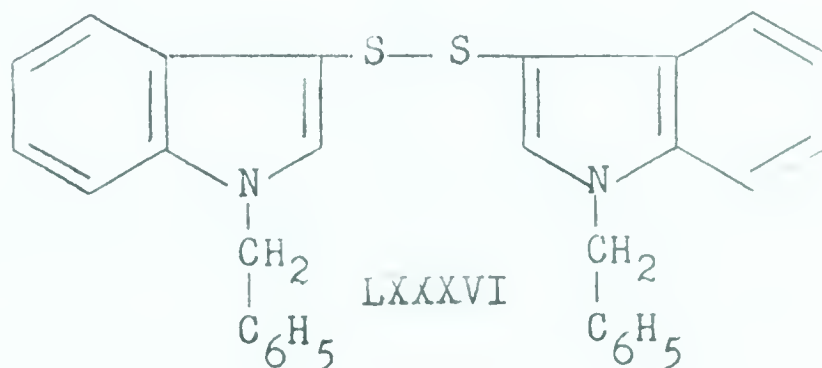
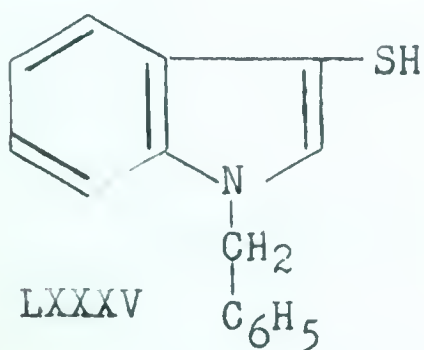


when they used ethyl bromoacetate in place of 2,4-dinitrochlorobenzene, they obtained 3,3'-diindolyl disulphide as the main product, with only a trace of the expected 3-indolylthioacetic acid (LXXXIV).





In an attempt to extend this sequence to the preparation of some 3-alkyl (or aryl) thioethers, 3,3'-diindolyl disulphide was reduced as described (76) and the reduction product treated with sodium hydroxide followed by two equivalents of benzyl iodide. A yellow crystalline compound was obtained melting at 151-153°C., analyzing for  $C_{15}H_{12}NS$ . Some unreacted diindolyl disulphide was also isolated. The compound  $C_{15}H_{12}NS$  gave a weak Ehrlich reaction suggestive of a free  $C_2$  or  $C_3$  position. Its infrared spectrum (Fig. 8, page 53) showed no absorption in the region 3300-3600  $cm^{-1}$  due to  $>N-H$  stretching characteristic of the indole structure (88). No absorption was observed in the region 2550  $cm^{-1}$  due to the sulphhydryl function (108). The nuclear magnetic resonance spectrum (Fig. 9, page 58) indicated aliphatic proton absorption at 4.96 $\tau$  and aromatic proton absorption in the region 2.49-3.30 $\tau$ . The integrated areas of the peaks gave a ratio of aromatic to aliphatic protons of 5:1. This is the ratio required for 3-mercapto-N-benzylindole (LXXXV), neglecting the sulphhydryl proton, or for N,N'-dibenzyl-3,3'-diindolyl disulphide (LXXXVI).









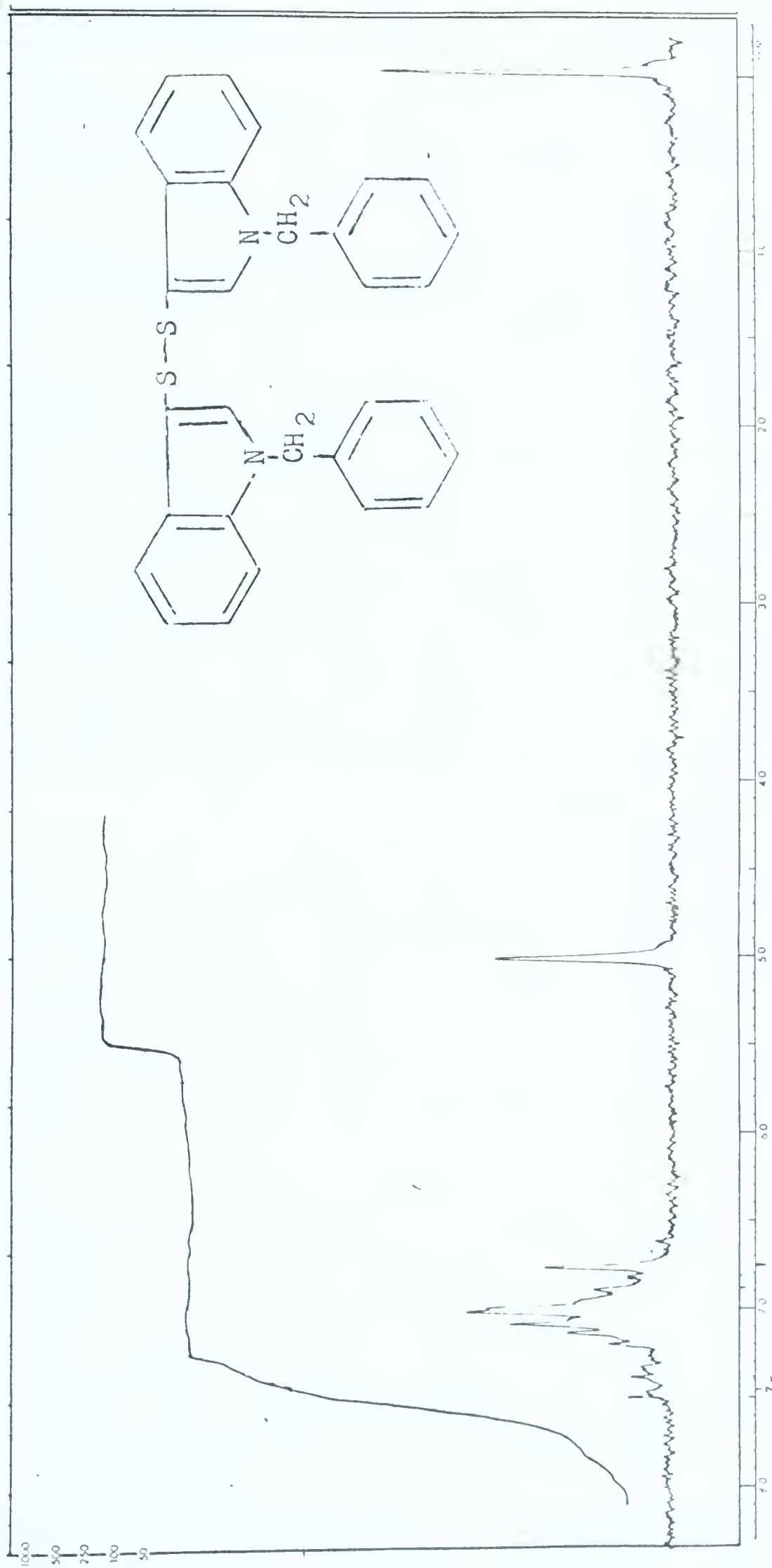


Fig. 9. N.M.R. Spectrum of N,N'-Dibenzyl-3,3'-Diindolyl Disulphide  
(Solvent, Carbon Disulphide. Referred to Tetramethylsilane.)



Structure (LXXXV) was rejected on the basis of the lack of absorption in the infrared region of  $2550\text{ cm}^{-1}$ , characteristic of the  $\text{—S—H}$  group, as well as absence of a signal in the n.m.r. spectrum due to a mercapto function. Chamberlain (109) gives the range of  $8.4\text{--}8.8\tau$  for the absorption of sulphhydryl protons of aliphatic thiols and  $6.4\tau$  for the signal due to the  $\text{—SH}$  proton of thiophenol. Furthermore lack of solubility of the compound  $\text{C}_{15}\text{H}_{12}\text{NS}$  in base argued against structure (LXXXV).

When the substance  $\text{C}_{15}\text{H}_{12}\text{NS}$  was treated with active Raney nickel in refluxing absolute ethanol for 24 hours, the compound N-benzylindole was produced, identified by melting point, mixed melting point and infrared spectrum. Authentic N-benzylindole was prepared for this purpose by the method of Hans Plieninger (110).

On the basis of the above evidence, structure (LXXXVI) (N,N'-dibenzyl-3,3'-diindolyl disulphide) was accepted for the compound whose analysis gave the empirical formula  $\text{C}_{15}\text{H}_{12}\text{NS}$ .

Snyder and Grant (76) have noted the extreme ease with which 3-mercaptoindole forms 3,3'-diindolyl disulphide, and indeed attempts to form this by reduction of the disulphide, followed by reaction with an active halide, usually gave back the disulphide except in the case cited above in which 3-(2,4-dinitrophenylthio)-indole (LXXXIII) was formed. It is interesting that in this case Snyder and Grant obtained S-arylation, but with benzyl iodide we obtained only N-benylation.

This synthetic approach to 3-alkylthioindoles was abandoned due to (a) the failure of Snyder and Grant's (76) attempt to form



3-indolylthioacetic acid in any significant amount, (b) the complication of preferred reaction at the nitrogen atom of the pyrrole ring found in our work, (c) and especially the undesirable physiological effect of 3,3'-diindolyl disulphide. This latter compound was found to be a highly potent general allergenic substance and in minute amounts caused urticaria, edema and finally a serious case of serum sickness, symptoms of allergic reactions. Even with careful manipulation in a fume hood, and avoidance of any bodily contact, these allergic symptoms appeared, requiring medical attention. The compound is extremely interesting from a medical point of view and supplies a means of inducing allergic response in rabbits and guinea pigs as well as humans. This aspect is under investigation elsewhere (Dr. T. H. Aaron, Baker Clinic Edmonton) and will be reported in the appropriate journal. It is interesting that the potent physiological effect is completely eliminated when the compound is converted to its N,N'-dibenzyl derivative.

It is also interesting that in the reaction of N-benzoyl-3-bromoindole at least one of the products not yet isolated, produces the same allergic symptoms. It is now suspected that the active agent responsible might be 3,3'-diindolyl disulphide. The complicated nature of the reaction with N-benzoyl-3-bromoindole and mercaptans may well produce traces of the offending disulphide.

## 2. Reactions Involving Indole Magnesium Halides in Attempts to Produce Alkylthioindoles.

A. The Reaction of Indolemagnesium Bromide with Ethylsulphenyl Chloride.







The reaction of N-benzoyl-3-bromoindole with mercaptans in the presence of potassium carbonate in the solvent dimethylformamide gave a strong indication that one of the products was 3-ethylthioindole. In order to verify this by comparison with an authentic sample of the thioether, the latter's preparation by another route was undertaken. To our knowledge, the literature gives no report of this compound.

It is known that sulphenyl chlorides react with Grignard reagents to yield thioethers (26-28), as shown below. Accord-



ingly an ethereal solution of ethyl sulphenyl chloride (26, 111) was added slowly to indolylmagnesium bromide at  $-10^{\circ}\text{C}.$ . The reaction mixture afforded several products which could be isolated and identified, as well as a number (at least 3) which as yet have not yet been separated and clarified. The presence of these unknown substances was shown by G.L.C. and by thin layer chromatography. Isolated from this reaction were the following compounds: 3,3'-diindolyl sulphide, 3-ethylindole, indole and ethyl mercaptan. Diethyl disulphide was indicated in the G.L.C. chromatogram, while 3,3'-diindolyl was indicated by means of thin layer chromatography. Gas-liquid chromatography\* gave evidence for the presence of 3-ethylthioindole, by the appearance of a peak with retention time characteristic of that for authentic 3-ethylthioindole. However since no 3-ethylthioindole was isolated, there is no conclusive evidence that 3-ethylthioindole

\*Carried out on two columns.

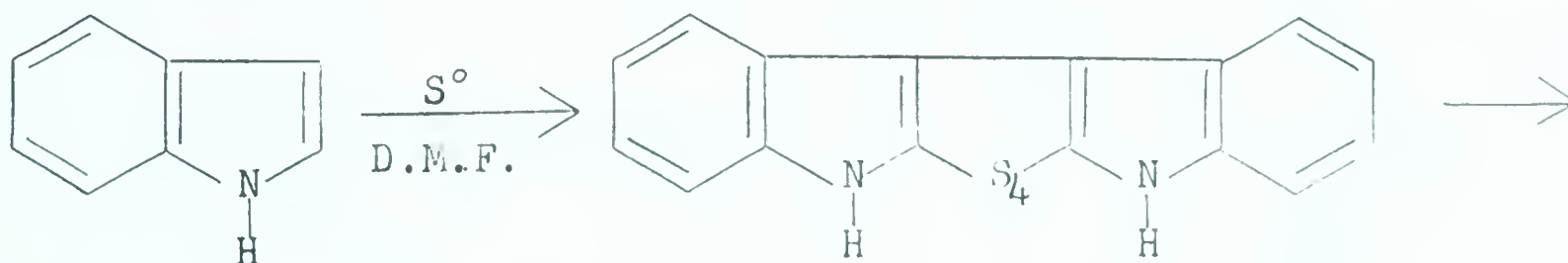


was in fact present. Thin layer chromatography also gave a spot which had the same  $R_f$  value as authentic 3-ethylthioindole.

Addition of ethanolic mercuric chloride to the ether extract of the reaction mixture (freed of ethyl mercaptan), or to traces of suspected 3-ethylthioindole collected from G.L.C., gave the readily identifiable ethylthiomericuric chloride. This evidence in total thus indicates strongly that 3-ethylthioindole is one of the products.

Here again a substance with powerful allergenic action was produced since the same physiological symptoms were experienced by the worker as described for the reaction involving mercaptans and N-benzoyl-3-bromoindole. This fact restricted somewhat the amount of work done on this phase of the problem.

Identification of the isolated compounds was made by comparison of their melting points, boiling points, infrared spectra and nuclear magnetic resonance spectra with those of authentic compounds. The method of Madelung and Tencer (73), involving the reaction of indole magnesium bromide with sulphur, was employed to synthesize 3,3'-diindolyl sulphide. A sample of 3-ethylindole was prepared by a modification of the method of Korizynski et al (105). Indole and diethyl disulphide were obtained commercially. 3,3'-Diindolyl was prepared according to the directions of Carpenter, Grant and Snyder (112) by the sequence shown below:

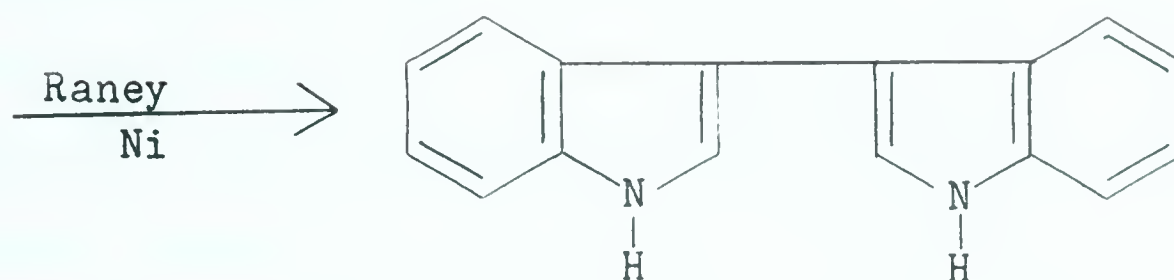


D.M.F. = Dimethylformamide

LXXXVII



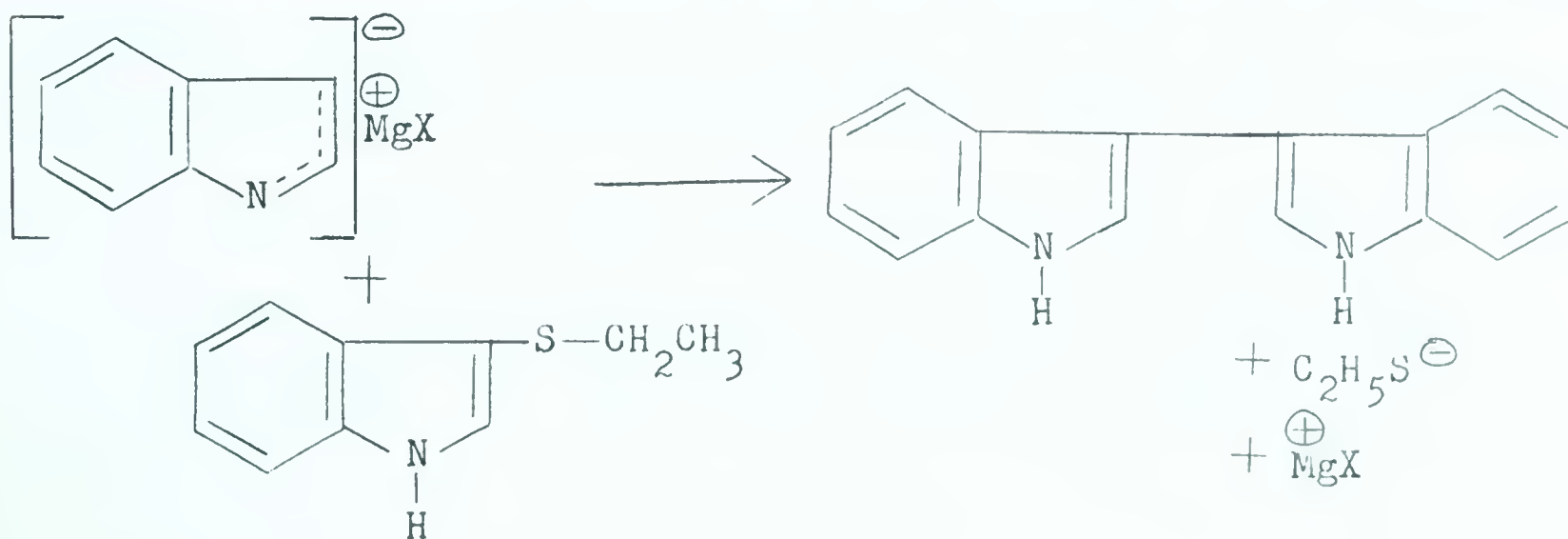




LXXXVIII

Diindolyl shows very strong blue-white fluorescence, first described by Gabriel et al (113). The characteristic colour reaction with Ehrlich's reagent and the fluorescence of diindolyl supplied evidence for its presence as observed by thin layer chromatography.

The origin of the 3,3'-diindole in the reaction of the indole Grignard reagent and ethyl sulphenyl chloride was investigated. The indole used in the preparation of the Grignard reagent was shown to be free from 3,3'-diindolyl, since only one spot characteristic of indole itself was found in a thin layer chromatogram of the indole. The extremely high sensitivity of this technique would permit the detection of even minute amounts of impurities. The possibility of a reaction between 3-ethylthioindole and indole magnesium bromide (see below) leading to the formation

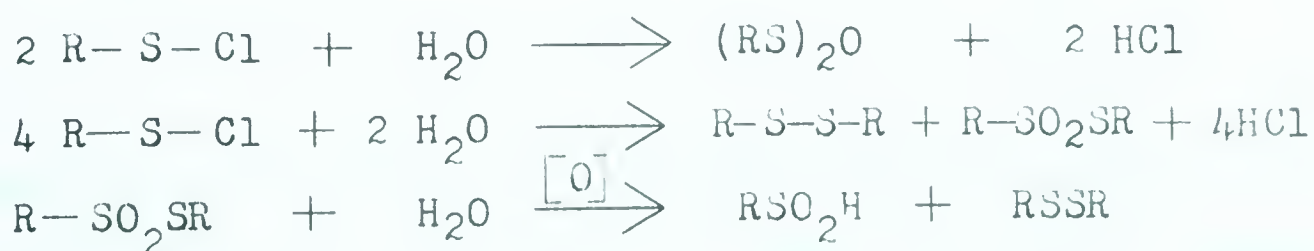






of diindolyl was eliminated since no reaction occurred between 3-ethylthioindole and either the mono- or di- Grignard reagent obtained from indole. (Such a reaction would have accounted nicely for both the diindolyl and ethyl mercaptan and was considered because it is known that Grignard reagents are capable of cleaving ethers, although usually at higher temperatures (128)). Only unchanged starting materials were recovered in good yield. However when a solution of indolemagnesium bromide was prepared and stirred for 24 hours with no special provision for the exclusion of air, and the reagent decomposed by cautious addition of water, followed by acetic acid, 3,3'-diindolyl was obtained as one of the products of the reaction as shown by thin layer chromatography. The bulk of the product was unreacted indole, but at least 9 other indolic substances were formed in small amounts as shown by the separate spots developed by Ehrlich's reagent on the thin layer chromatogram. From this it is evident that 3,3'-diindolyl could quite likely have been formed in our reaction, in the small amounts apparently present, by some oxidation reaction involving the Grignard reagent.

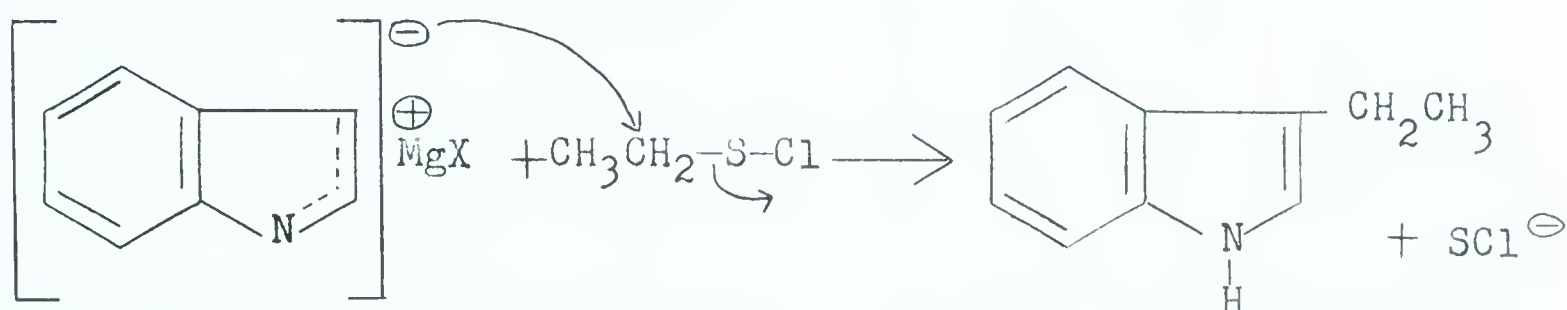
The formation of ethyl mercaptan does not occur by hydrolysis of the unreacted sulphenyl chloride during the isolation procedure since hydrolysis of sulphenyl chlorides yields a mixture of substances indicated below (114). Apparently, according



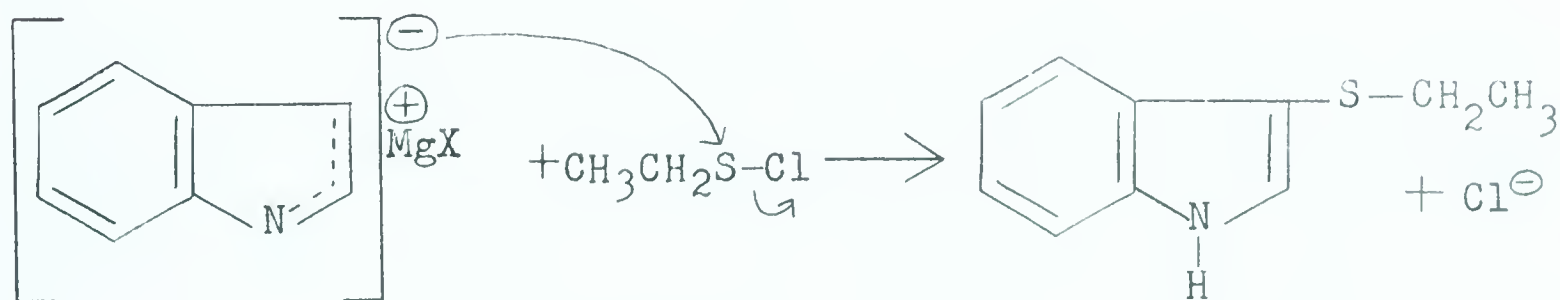


to the literature, no mercaptan is produced. It is known that sulphenyl halides can be reduced to the species  $R-S-S-R$  (115). It is thus possible that the oxidizability of indole in the form of the Grignard reagent (116) might be responsible for the reductive formation of diethyl disulphide and its subsequent conversion to ethyl mercaptan.

The mode of formation of 3-ethylindole in this reaction is not at all clear. This substance was isolated by distillation of the ether extract of the reaction mixture, as well as by addition of picric acid to this ether extract and precipitation of the picrate (m.p.  $142-143^{\circ}\text{C.}$ ), identical to the picrate of authentic 3-ethylindole. Its formation via a reaction such as



in competition with the known reaction

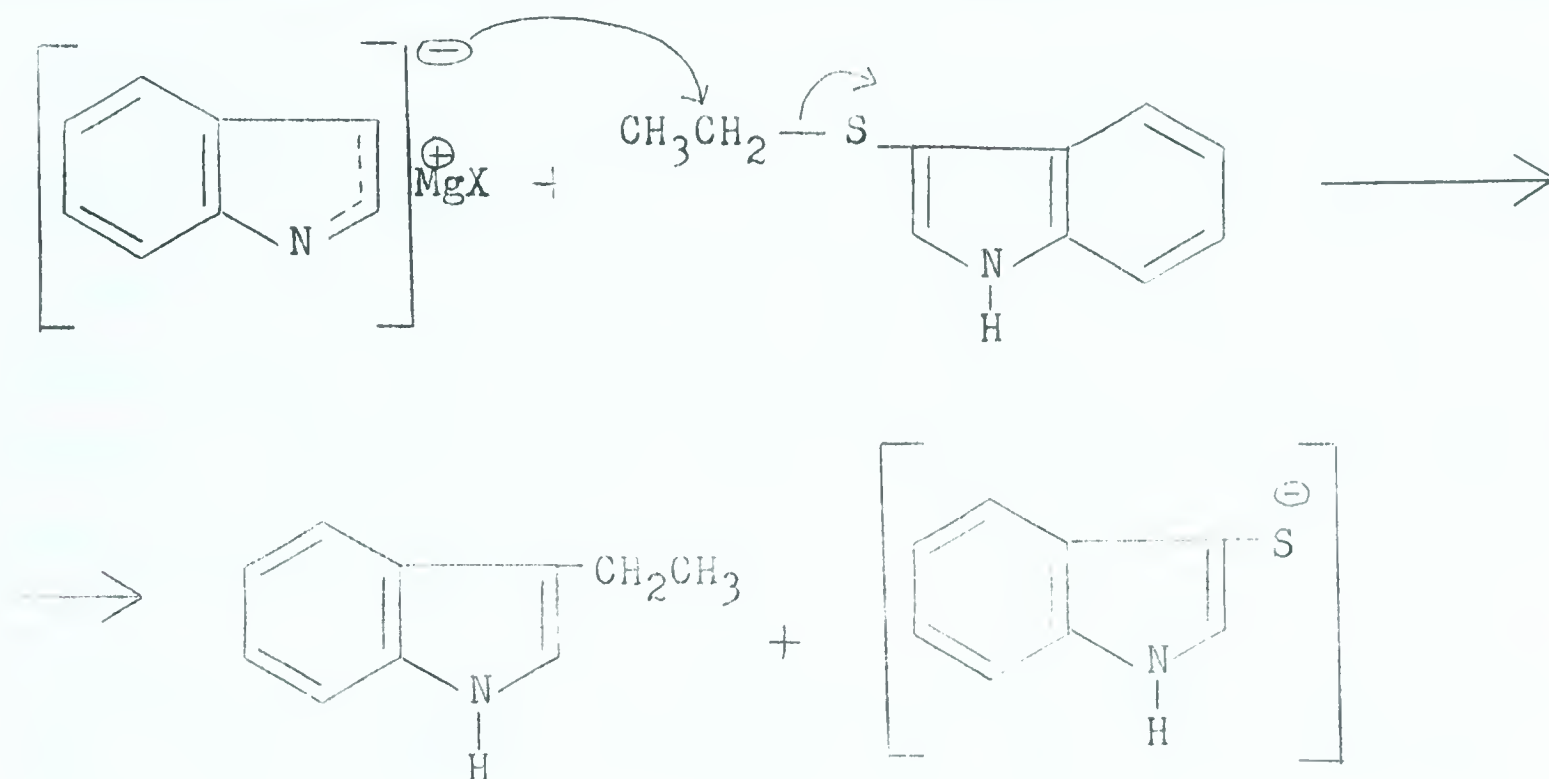


to produce the thio ether was considered unlikely since in a separate experiment it was shown that phenylmagnesium bromide and

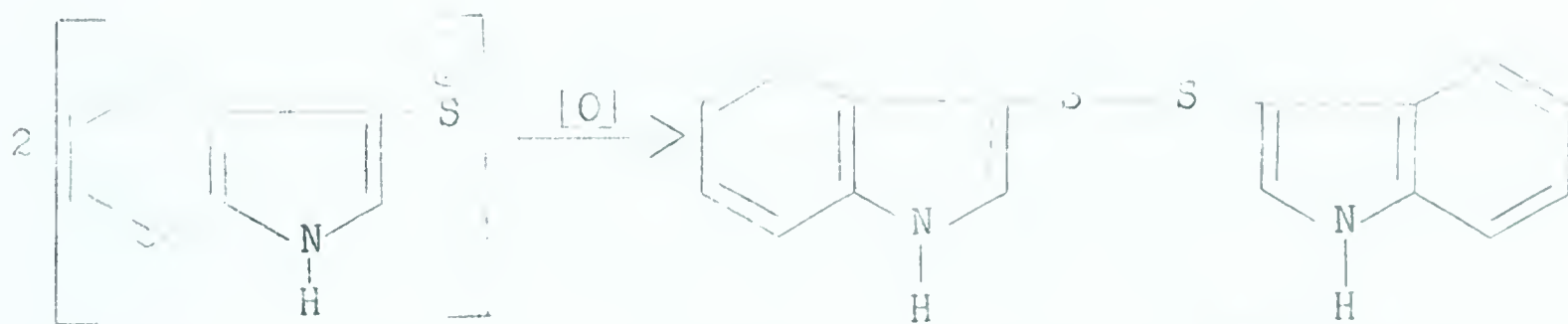


ethylsulphenyl chloride gave only the ethyl phenyl thioether and no ethylbenzene. The di-Grignard obtained from p-dibromobenzene also failed to yield any alkylated benzene when treated with ethylsulphenyl chloride.

The possibility that a reaction mechanism such as that shown below was examined by allowing indole magnesium bromide to react



with authentic 3-ethylthioindole. The ready and almost inevitable oxidative conversion of the 3-indolylthio anion to 3,3'-diindolyl disulphide, described in the work of Snyder and Grant



(76), and the fact that the physiological activity\* of one (or more) product of the reaction was experienced suggested that such a reaction might be possible. However from the reaction of

\*Allergenic.

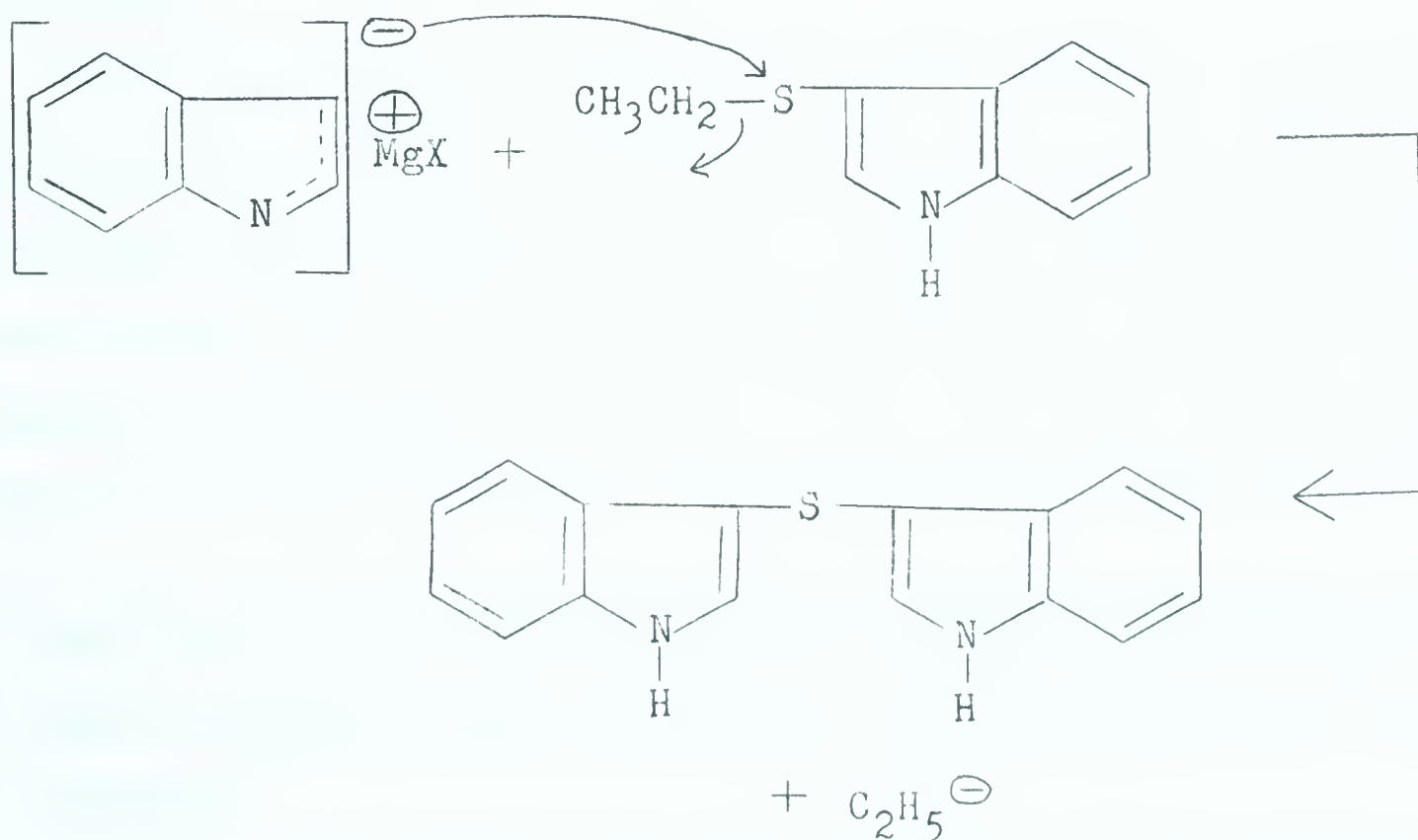






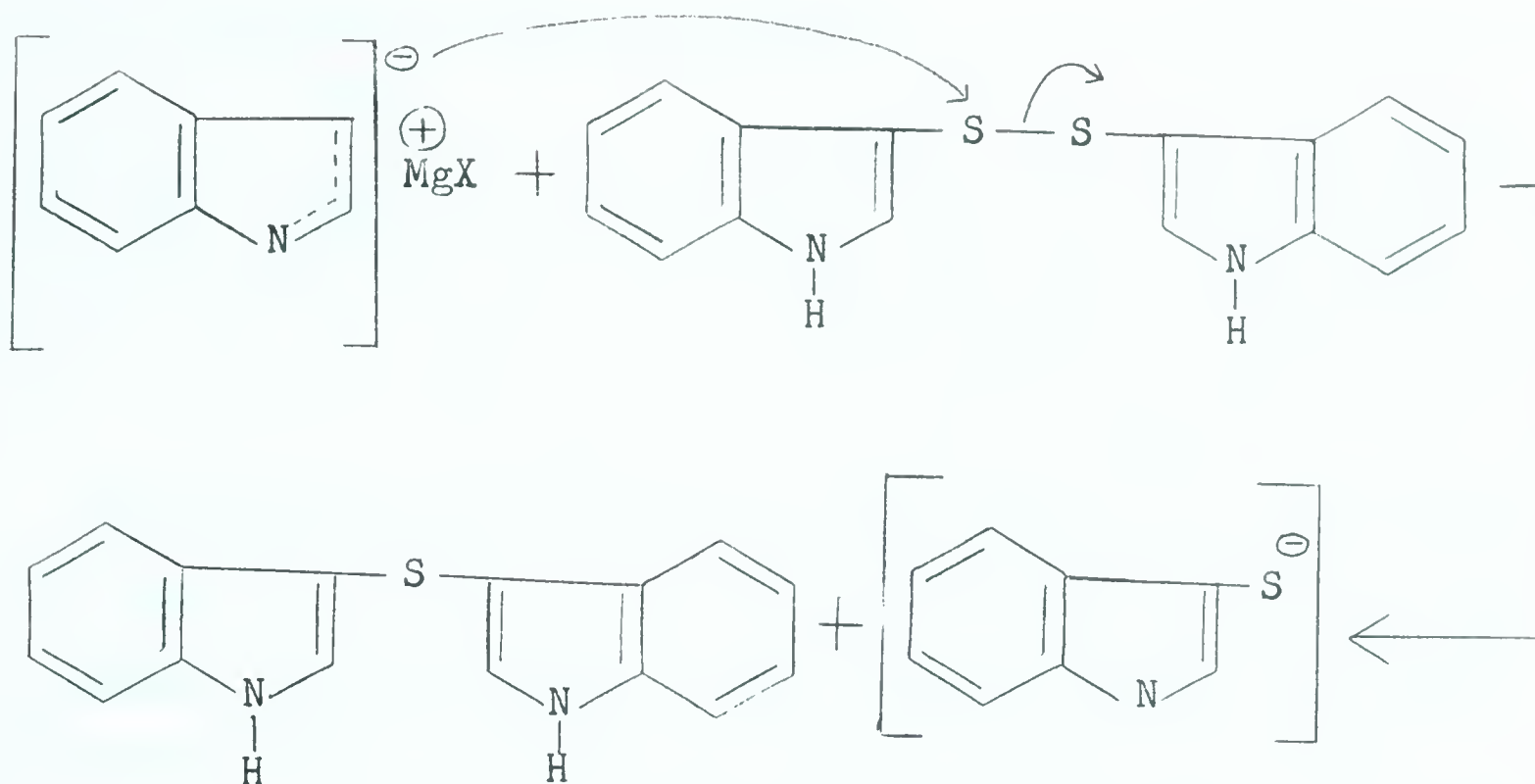
3-ethylthioindole with indolemagnesium bromide, under conditions similar to those used in the original sequence, only unchanged thioether and indole would be isolated. Furthermore, although the highly insoluble nature of 3,3'-diindolyl disulphide in benzene allows it to be readily isolated as a precipitate upon dilution of the reaction mixture with benzene, none was isolated from the indole Grignard reaction with ethylsulphenyl chloride.

The method of formation of 3,3'-diindolyl sulphide in the reaction of indolemagnesium bromide with ethyl sulphenyl chloride is also not understood. Since no reaction occurred between 3-ethylthioindole and indolemagnesium bromide, or the indole di-Grignard, formation from these two reagents by the route designated below is untenable.



The possibility that the 3,3'-diindolyl sulphide could be formed from a reaction between the indole Grignard and 3,3'-diindolyl





disulphide was ruled out since in an attempt to bring about a reaction between these two reagents only starting materials were recovered.

It is quite obvious that the reaction between indolemagnesium bromide and ethylsulphenyl chloride is not a practical means for producing 3-alkylthioindoles. For this reason, as well as the adverse physiological effect experienced by the worker on exposure to the reaction mixture, this route was abandoned, although here again a number of problems remain unsolved.

#### B. The Reaction of Indolemagnesium Bromide with Sulphur and the Mode of Formation and the Structure of the Diindolyl Sulphide Produced.

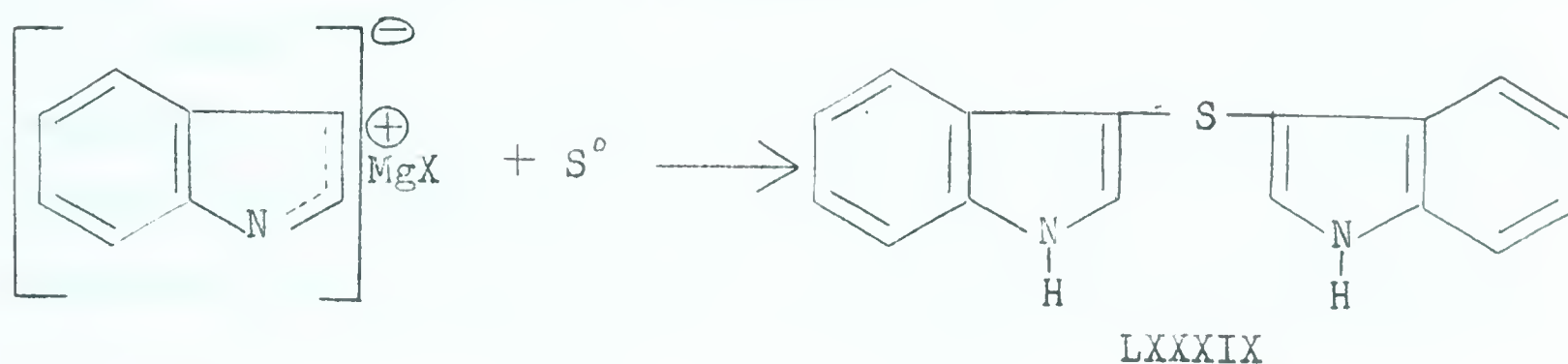
The reaction between equimolar amounts of indolemagnesium bromide and sulphur, as described by Madelung and Tencer (73) produces a yield of a substance designated by these authors as



The first part of the report deals with the general principles of the investigation. It is divided into two main sections: a description of the apparatus and a description of the method of observation. The second part of the report deals with the results of the investigation. It is divided into two main sections: a description of the results of the observations and a description of the results of the calculations. The third part of the report deals with the conclusions of the investigation. It is divided into two main sections: a description of the conclusions of the observations and a description of the conclusions of the calculations.

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the 3,3'-diindolyl sulphide (LXXXIX).



The structure as accepted does not appear to be established on a completely sound basis. The aim of these authors (73) was to produce 3-mercaptoindole by the reaction of the indole Grignard with sulphur. However no alkali-soluble material was obtained although the same reactions, applied to Grignard reagents from alkyl halides (118) or from aryl halides (119), gave the mercaptan in yields as high as 80% if an atmosphere of nitrogen was employed and excess sulphur avoided to prevent oxidation of the mercaptan to the disulphide (119,120).

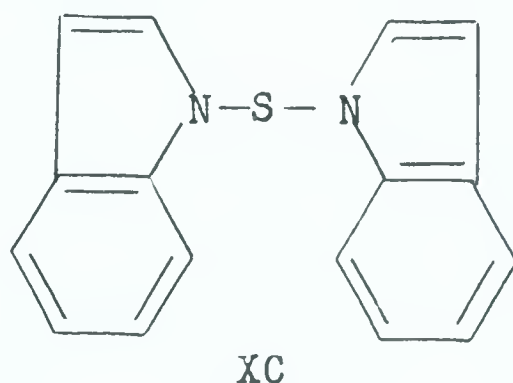
The mode of formation of the unexpected sulphide was not determined by Madelung and Tencer, but Wuyts and Cosyness (117) had obtained, by treating an ethereal solution of phenylmagnesium bromide with sulphur, not only the expected thiophenol and diphenyl disulphide but also a small amount of diphenyl sulphide. Wuyt and Cosyness also showed that the diphenyl sulphide might feasibly arise from a secondary reaction of phenylmagnesium bromide on diphenyl disulphide. It was shown that diphenyl disulphide reacted with phenylmagnesium bromide to produce diphenyl sulphide. The formation of diindolyl sulphide might also arise in this way. This possibility was examined as described earlier on page 67, with some additional detail on pages 80 and 81.







Madelung and Tencer (73) found that their diindolyl sulphide was unusually inert, being stable to oxidation by potassium permanganate, to boiling potassium hydroxide solution and inactive towards acetic anhydride or nitrous acid. On this basis they suggested the possibility of the structure (XC). Nevertheless

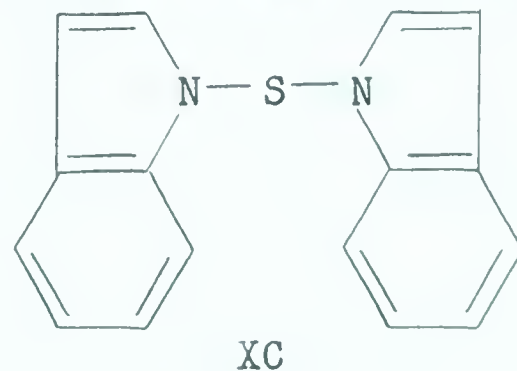
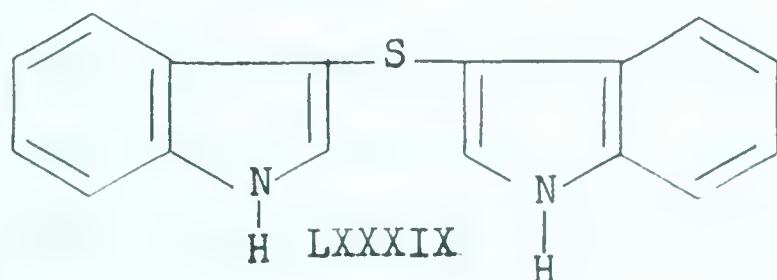


the structure (LXXXIX) (3,3'-diindolyl sulphide) has been accepted (75, 120), presumably on the basis of known reactions of indole magnesium salts (123) yielding 3-substituted derivatives.

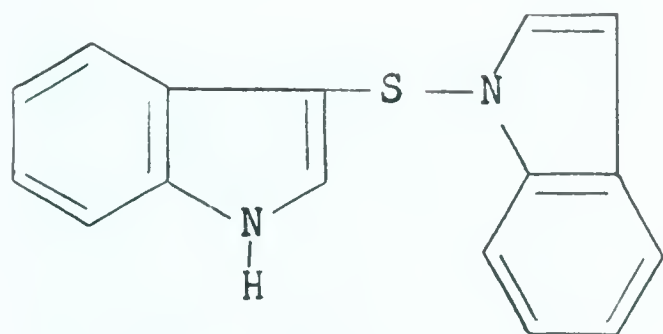
Since in this laboratory an indole sulphide was isolated from the reaction of indole magnesium bromide with ethylsulphenyl chloride, correctly analyzing for diindolyl sulphide and showing an infrared spectrum identical with that of the compound obtained by the method of Madelung and Tencer, it was felt that the structure should be placed on a firm basis.

### Structural Studies

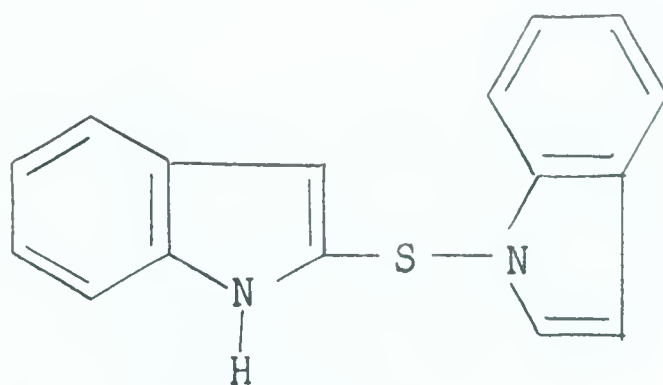
The possible structures agreeing with the elemental analytical data are shown below.



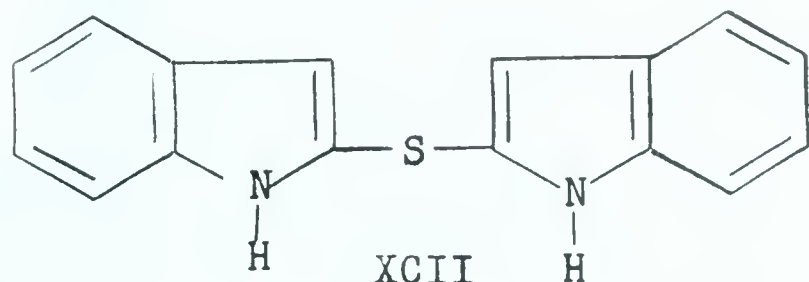




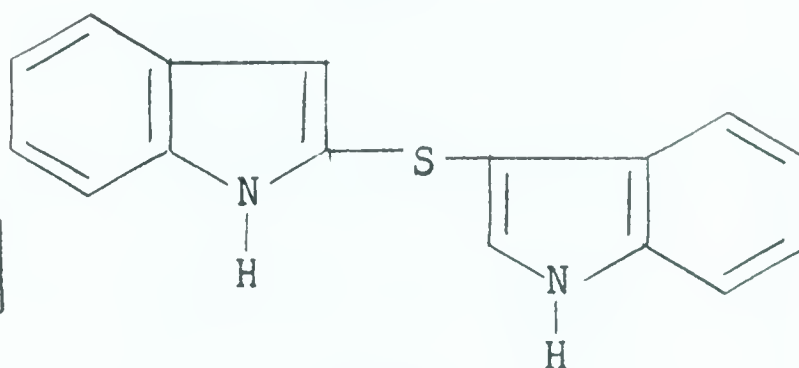
XCIa



XCIb



XCII



XCIII

In order to distinguish between the structures both infra-red and n.m.r. studies were made.

Due to the generally poor solubility of the diindolyl sulphide (120) in suitable solvents, the infrared spectrum was obtained in a nujol mull. This showed a sharp doublet at 3395 and 3410  $\text{cm}^{-1}$  (Fig. 10, page 72) in the region expected for indole  $\text{>N-H}$  stretching (88). The presence of the absorption eliminates structure (XC).

Exchange of the hydrogen on nitrogen for deuterium (a reaction very easily accomplished by the usual procedure of repeated treatment of the sulphide with  $\text{D}_2\text{O}$  in pyridine or acetone) eliminated this doublet in the infra red spectrum (Fig. 11, page 72) as well as the doublets at 1405 and 1410  $\text{cm}^{-1}$ , and 1085 and 1095  $\text{cm}^{-1}$  and also the bands at 1105 and 1118  $\text{cm}^{-1}$ . A new band appeared at 2535  $\text{cm}^{-1}$ , accompanied by a lesser band at 2522  $\text{cm}^{-1}$ .





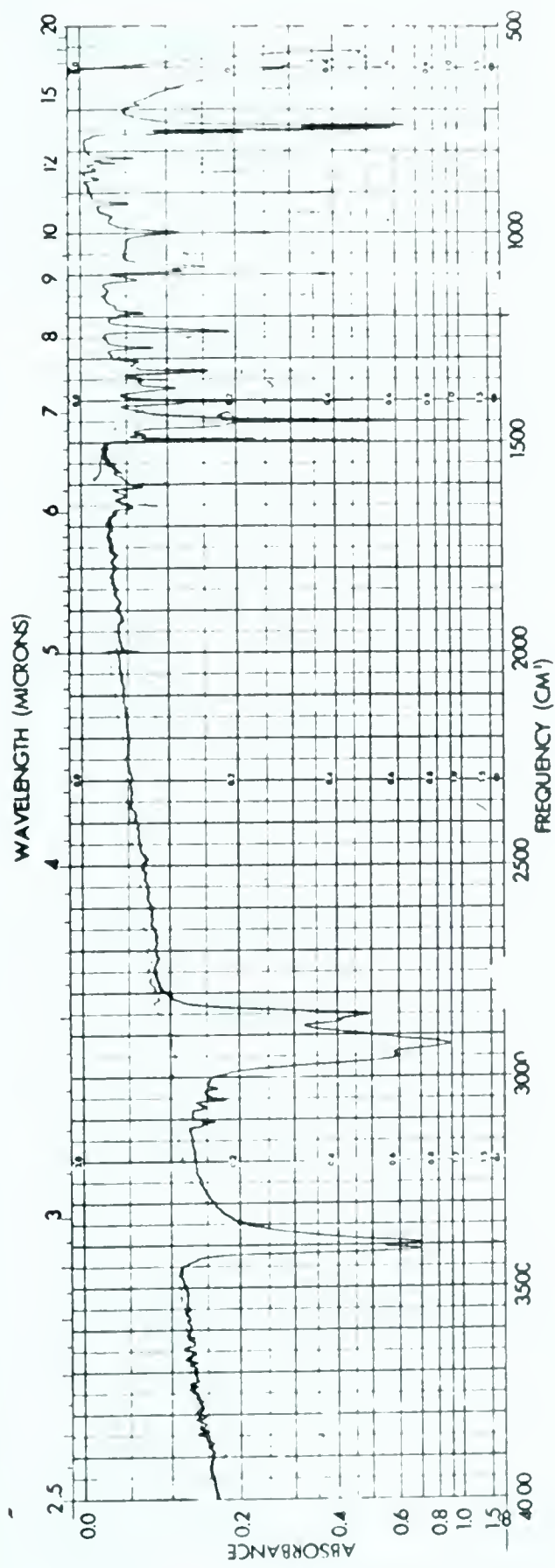


Fig. 10. I.R. Spectrum of 3,3'-Diindolyl Sulphide.

(Nujol mull).

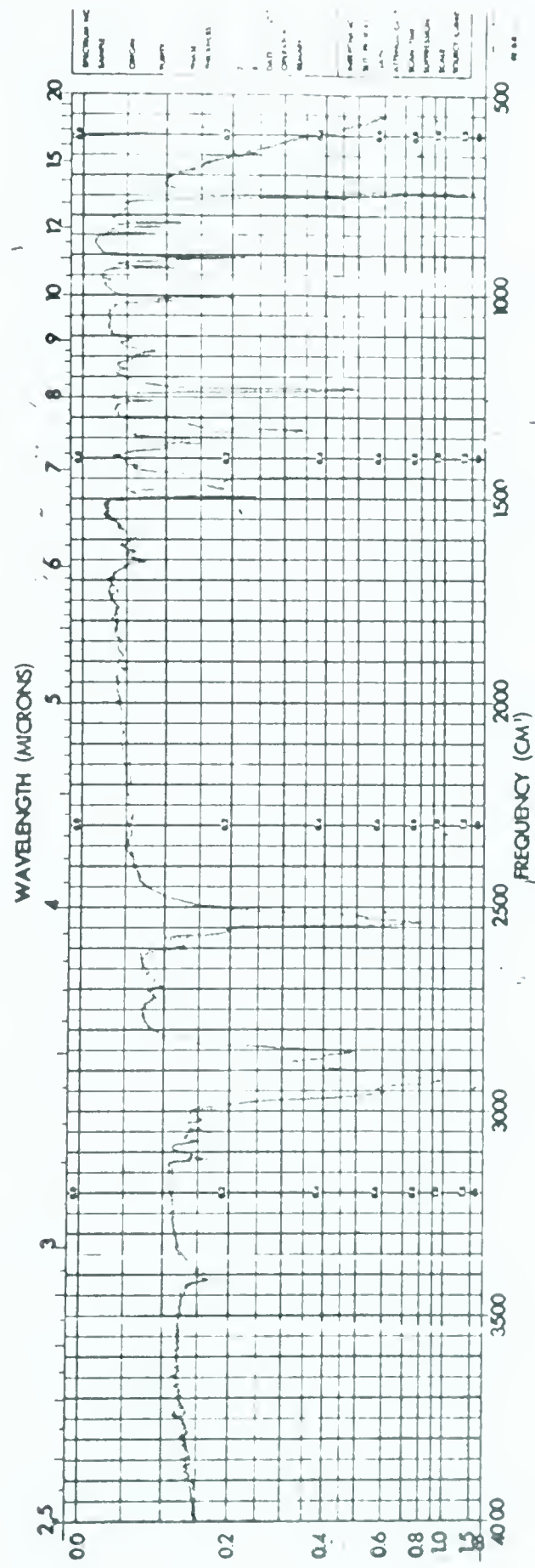


Fig. 11. I.R. Spectrum of N,N'-Dideutero-3,3'-Diindolyl Sulphide.

(Nujol mull).





along with a new doublet at 910 and 915  $\text{cm}^{-1}$ . This shift in absorption upon replacement of an hydrogen atom on nitrogen by deuterium is approximately that predicted by Hooke's law (122). The appearance of doublets in the infrared spectrum indicated the possibility of a structure such as (XCIII) containing two slightly different  $\text{>N-H}$  groups.

Nuclear magnetic resonance evidence however supported structure (LXXXIX). It has been shown by Witkop et al (121) that in  $\text{CDCl}_3$  solution, the  $\text{C}_2$  and  $\text{C}_3$  protons of indole absorb at  $\tau$  values of 3.32 and 3.62 respectively (referred to tetramethylsilane). Due to the solubility limitations of the diindolyl sulphide, acetone was chosen as the solvent for n.m.r. analysis, using tetramethylsilane as internal standard. In this solvent the  $\text{C}_2$  proton (or  $\text{C}_3$  proton) was shifted farther downfield due to the combined inductive effect of the sulphur and nitrogen atoms, and appeared as a doublet at  $\tau=2.43$ ,  $J=2$  c.p.s., the integrated area of which corresponded to two protons (Fig. 12, page 74). This assignment was made since replacement of the  $\text{>N-H}$  by  $\text{>N-D}$  (Fig. 13, page 75) caused the doublet to collapse into a sharp singlet, whose integrated area was equivalent to two protons. The disappearance of splitting provides evidence of coupling between the  $\text{>N-H}$  and the  $\text{C}_2$  (or  $\text{C}_3$ ) proton, and indicates that the protons are equivalent, thus eliminating structures (XCIIa and XCIIb) and (XCIII), and supporting structures (LXXXIX) and (XCII).

A decision between structures (LXXXIX) and (XCII) could be made by determining the extent of the change in chemical shift of the signals for the  $\text{C}_2$  (or  $\text{C}_3$ ) proton of indoles as one changes



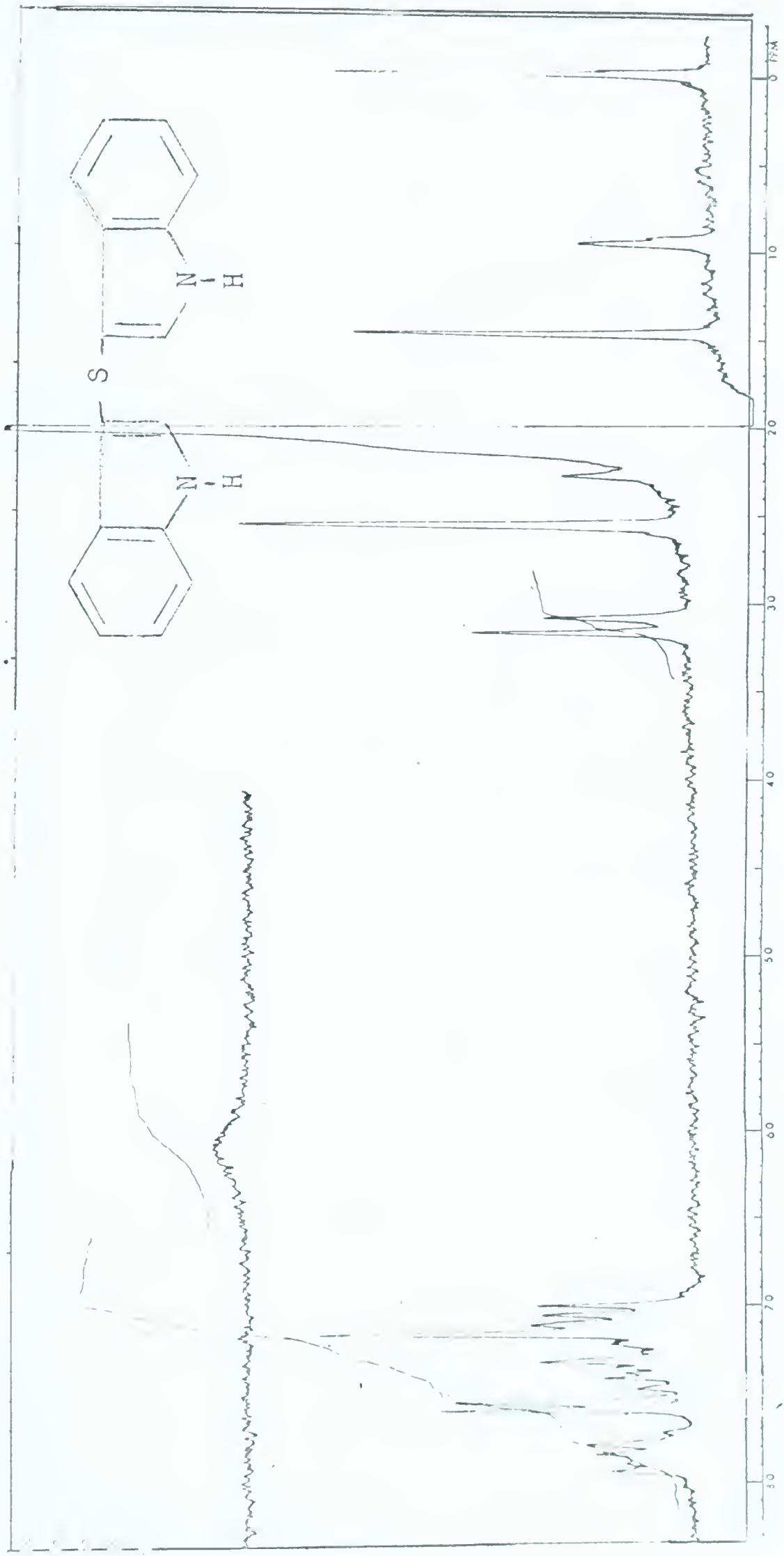


Fig. 12. N.M.R. Spectrum of 3,3'-Diindolyl Sulphide.  
(Solvent, Acetone. Referred to Tetramethylsilane.)



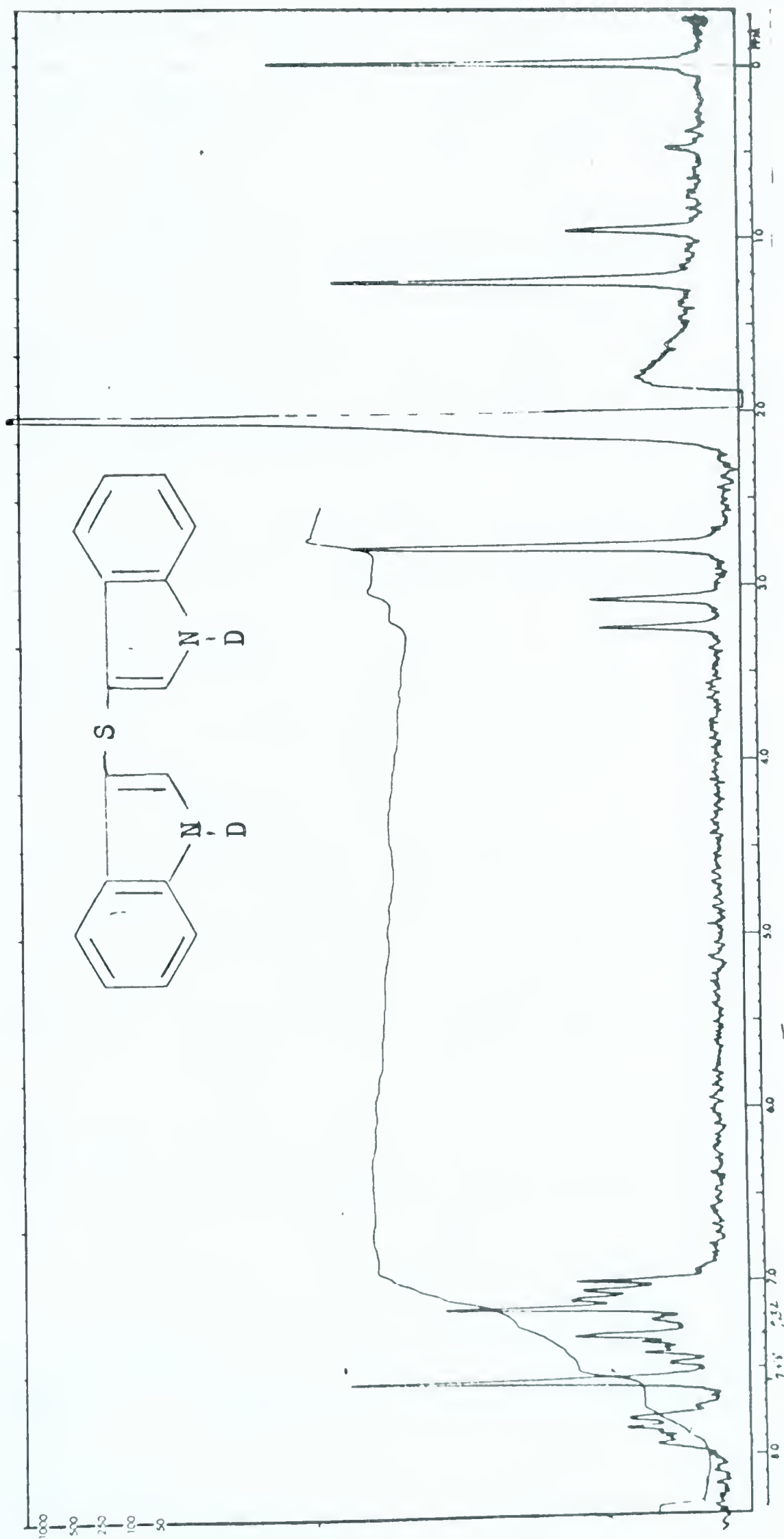


Fig. 13. N.M.R. Spectrum of N,N'-Dideutero-3,3'-diindolyl Sulphide.  
(Solvent, Acetone. Reference - Tetramethylsilane.)





from one solvent to another. It is known from work described later in this thesis, that the signal position of the  $C_2$  proton of indoles is markedly affected by solvent, while that of the  $C_3$  proton of indoles remains practically unchanged in various solvents. The poor solubility characteristics of the diindolyl sulphide limited the application of the technique somewhat, but was sufficiently useful to permit clear distinction between structures (LXXXIX) and (XCII).

The signals for the  $C_3$  protons of indole, ethyl indole-2-carboxylate and indole-2-carboxylic acid were found to be at nearly the same position in the three solvents dioxan, dimethyl sulphoxide and acetone. However the position of the  $C_2$  proton signals of indole, ethyl indole-3-carboxylate and indole-3-carboxylic acid were found to vary considerably in these solvents (see section on n.m.r. studies of 2- and 3- substituted indoles). In no case, in the pairs of solvents used was there more than a difference of 0.081' found for the  $C_3$  proton signal position. On the other hand, the  $C_2$  proton signal changed as much as 0.18 to 0.24 $\tau$ .

The signal positions for the  $C_2$  (or  $C_3$ ) protons of the diindolyl sulphide are shown in Table I.

TABLE I

Signal Positions of  $C_2$  (or  $C_3$ ) Proton of Diindolyl Sulphide

Solvent	Dioxan	Dimethyl Sulphoxide	Acetone
Signal (doublet)	2.66 J=2 c.p.s.	2.40 J=2 c.p.s.	2.43 J=2 c.p.s.



Since the difference in the signal position in dioxan and dimethyl sulphoxide is 0.26 $\tau$ , strong evidence for the adoption of the structure (LXXXIX) for the diindolyl sulphide is indicated.

The likelihood that the substance is a mixture of 3,3'-diindolyl sulphide and 2,2'-diindolyl sulphide is ruled out by the n.m.r. spectrum which shows one doublet, whose integrated area is equal to two protons, and the spectra which show a large shift in the position of this particular doublet as one changes from one solvent to another. (Figs. 14 and 15, pages 78 and 79). A mixture of the two sulphides mentioned would be expected to show two doublets which are reduced to two singlets upon deuteration, and of which one doublet would shift in position more than the other upon change of solvent.\* This was not observed.

The doublet observed for the  $\text{>N-H}$  stretching in the infrared spectrum of 3,3'-diindolyl sulphide requires comment. This  $\text{>N-H}$  doublet might be due to the interactions between neighboring molecules in the crystalline state causing band duplication (131). Such band duplication apparently disappears upon solvation, and in fact solvation of the sulphide in dioxane gave a single though somewhat broadened band at  $3300\text{ cm}^{-1}$  (Fig. 16, page 80). In methylene chloride the infrared spectrum of 3,3'-diindolyl sulphide, measured at high resolution, showed a single peak at  $3460\text{ cm}^{-1}$  (Fig. 17, page 80).

#### Experiments Regarding the Mode of Formation of 3,3'- Diindolyl Sulphide.

Some attempts were made to establish the route by which 3,3'-diindolyl sulphide could be formed in the reaction between

\*It is of interest to note that Reinecke et al. have recently observed a similar solvent effect (47).





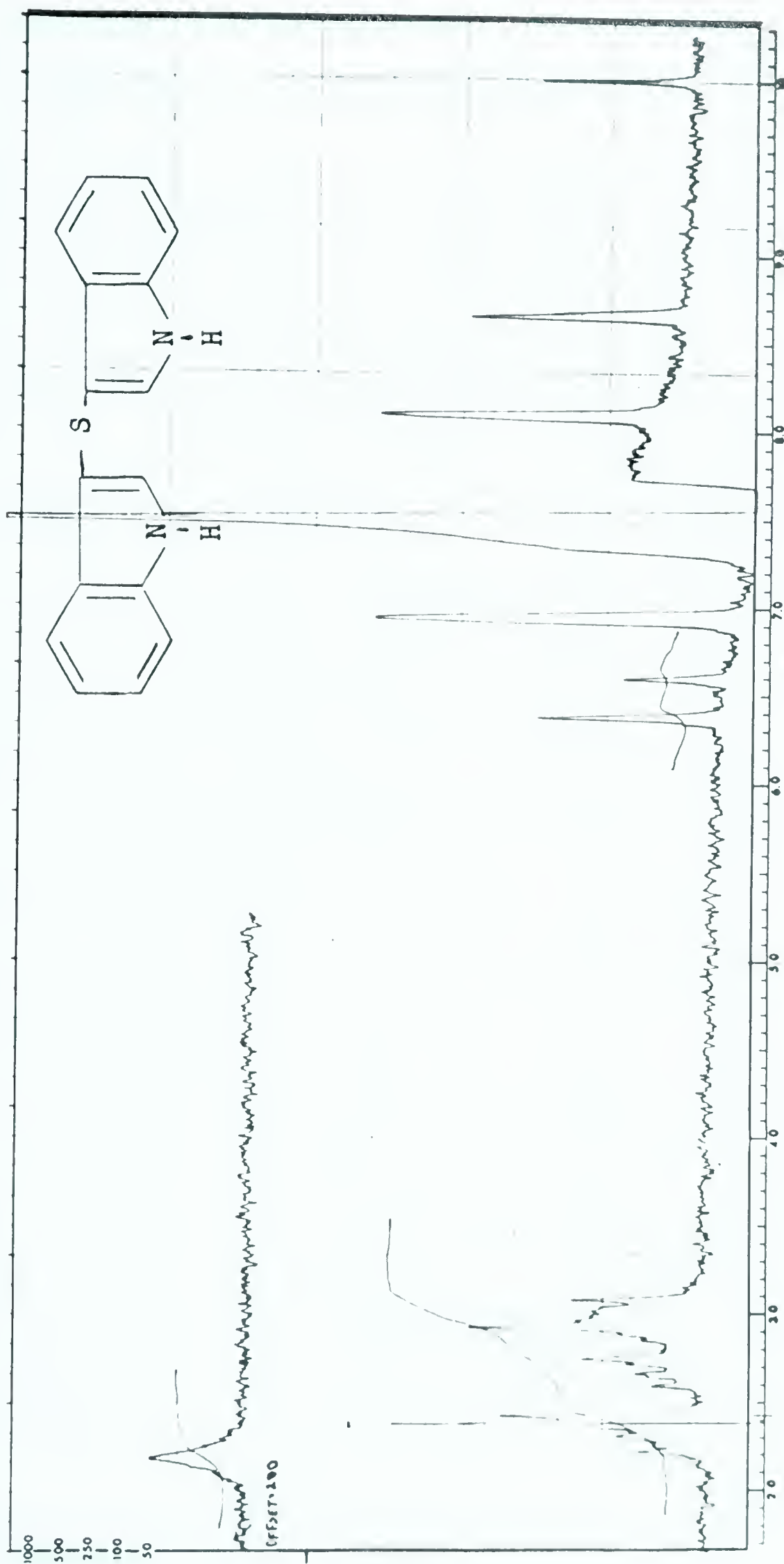


Fig. 14. N.M.R. Spectrum of 3,3'-Diindolyl Sulphide.

(Solvent, Dimethylsulphoxide. Reference - Tetramethylsilane.)





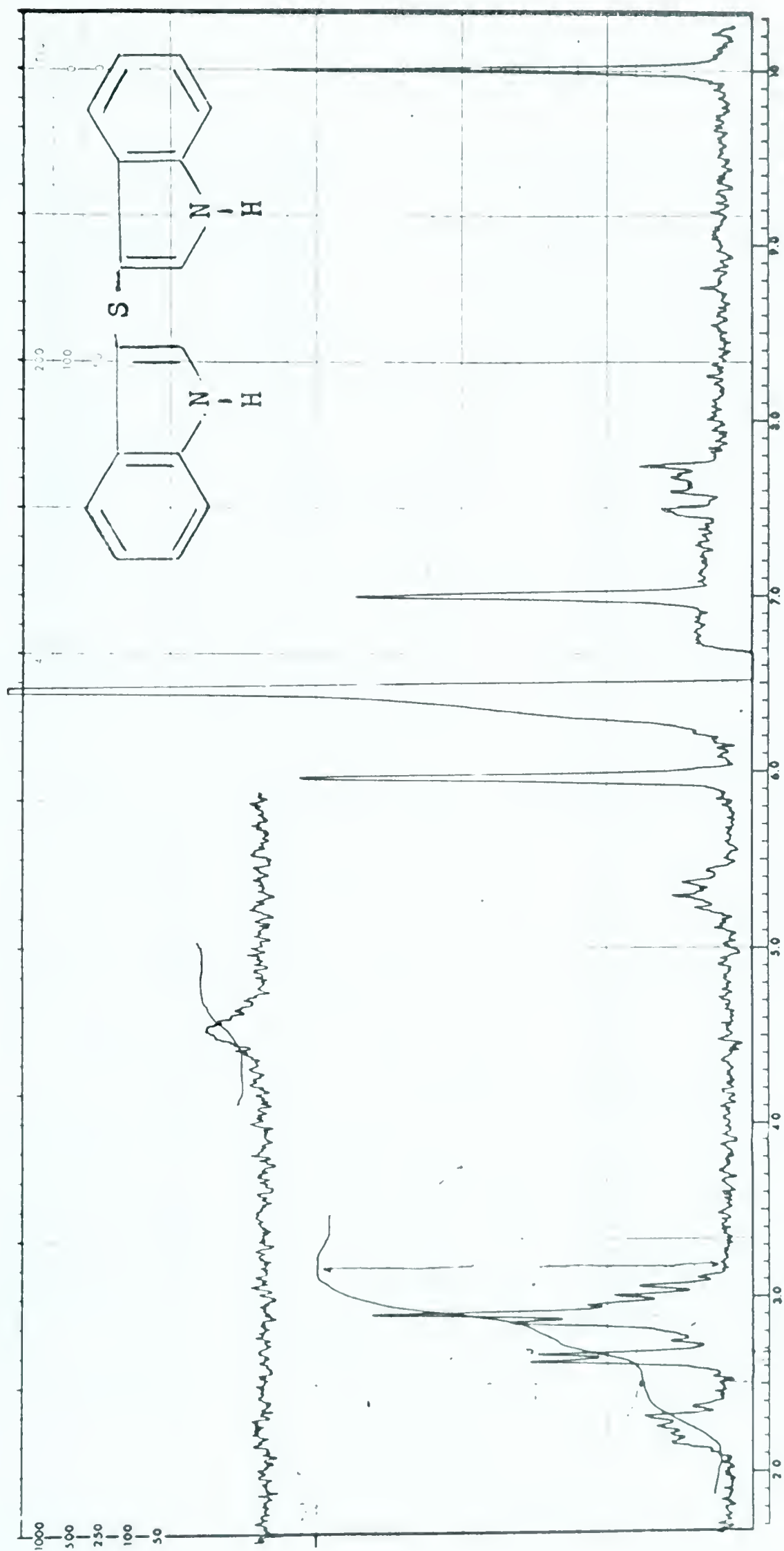


Fig. 15. N.M.R. Spectrum of 3,3'-Diindolyl Sulphide.  
(Solvent, Dioxan. Reference - Tetramethylsilane.)



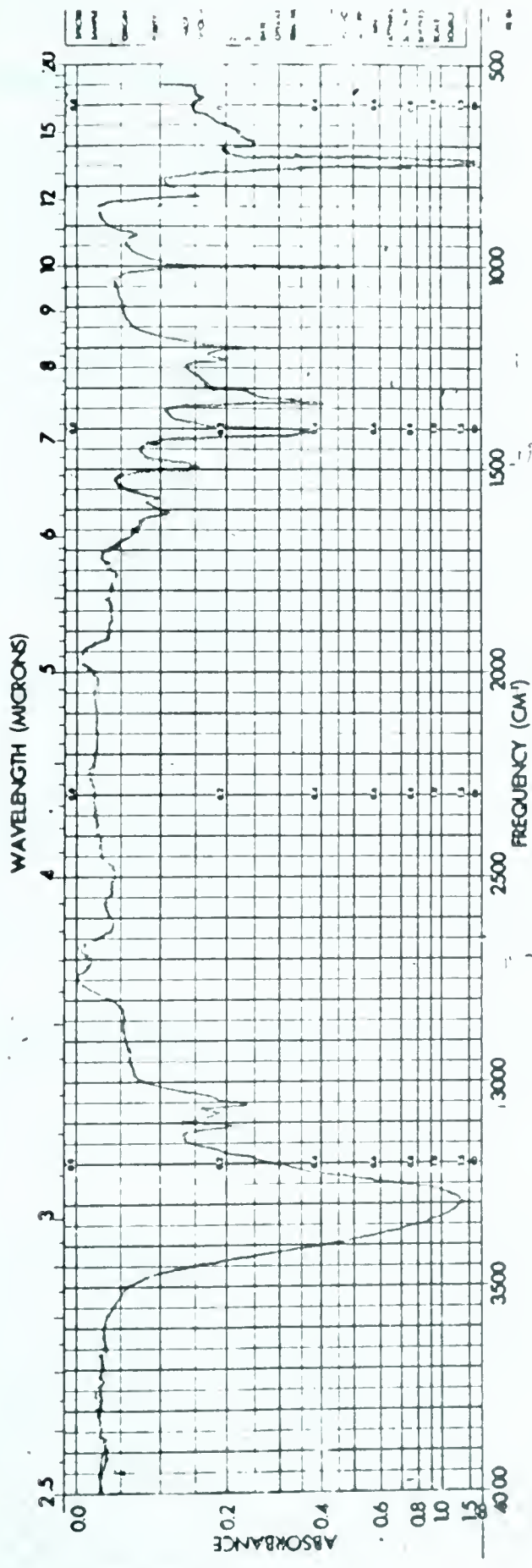


Fig. 16. I.R. Spectrum of 3,3'-Diindolyl Sulphide.  
(Solvent, Dioxan).

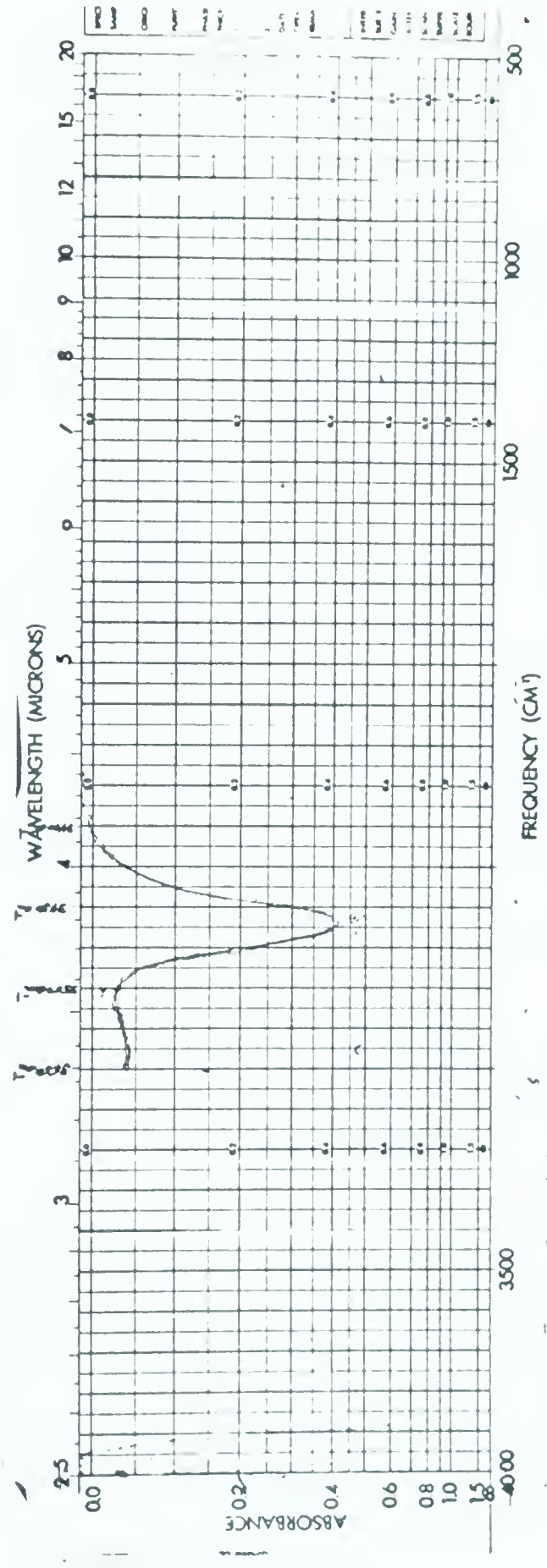


Fig. 17. Partial I.R. Spectrum of 3,3'-Diindolyl Sulphide.  
(Solvent, Methylene Chloride).



indole magnesium bromide and elemental sulphur. Following the suggestion which came from the work of Wuyts (117) that aryl magnesium halides reacted with diaryl disulphides to yield a diaryl sulphide and an arylthiomagnesium salt, this reaction was examined. This route appeared promising since diindolyl disulphide is extremely easily formed (76). However, as noted previously (page 67) this reaction did not occur, and only unchanged diindolyl disulphide was recovered in 74% yield.

### 3. Use of the Fischer Indole Synthesis in Obtaining 3-Alkylthioindole.

As described earlier (page 26), the Fischer indole synthesis has been successfully applied in the synthesis of 2-thioindoles (79). It was decided, therefore, to pursue this route as a more straightforward method to obtain 3-thioindoles.

Ethylthioacetaldehyde diethylacetal (XCIV) was synthesized



XCIV

according to the method of Berkofer and Storch (124) by the reaction of bromoacetaldehyde diethyl acetal with sodium ethyl mercaptide. This acetal, when heated with one equivalent of each of boron trifluoride etherate and phenylhydrazine in glacial acetic acid underwent a smooth, exothermic reaction.

The products of the reaction when chromatographed on neutral alumina (activity grade 1) using benzene as eluant, then distilled under vacuum yielded a light yellow oil analyzing for  $\text{C}_{10}\text{H}_{11}\text{NS}$ .





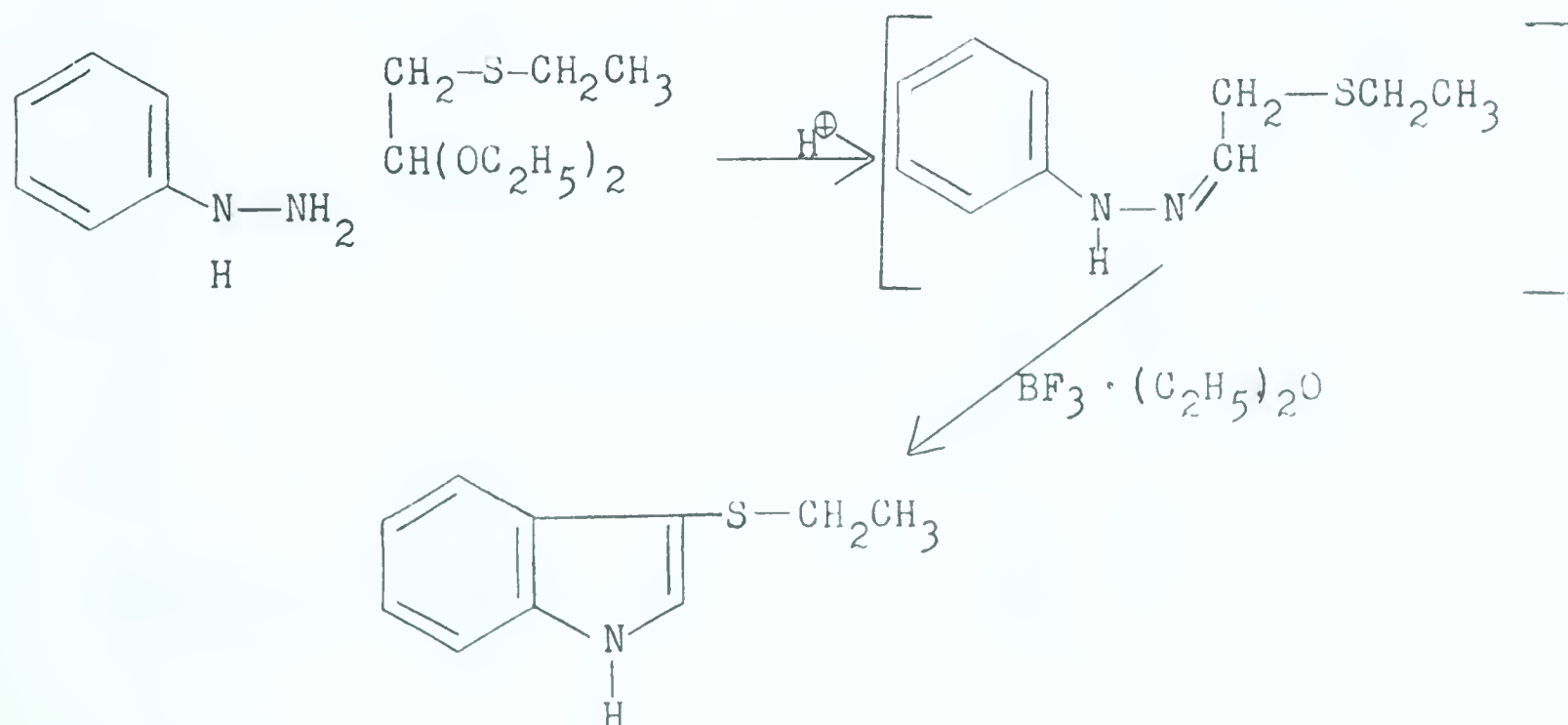


The compound reacted very slowly with the Ehrlich reagent, and this indicated an indole with a free C<sub>2</sub> or C<sub>3</sub> position. Infrared analysis indicated strong  $\text{>N-H}$  stretching at 3410 cm<sup>-1</sup> characteristic of indoles (88), and aliphatic hydrogen at 2915 and 2980 cm<sup>-1</sup> (Fig. 18, page 84). A nuclear magnetic resonance spectrum indicated a triplet at 8.8 $\tau$ \*, a quartet at 7.3 $\tau$ \* indicative of the CH<sub>3</sub>-CH<sub>2</sub> grouping. Aromatic hydrogen was observed at 2.0-3.0 $\tau$  (Fig. 19, page 83).

The C<sub>2</sub> proton of the indole was shifted downfield and buried among the aromatic hydrogen signals due to the combined inductive effects of the sulphur and nitrogen atoms.

Analysis of the compound by mass spectrometry yielded a molecular weight of 177. The empirical formula was calculated by the method described by Silverstein and Bassler (125) and found to be C<sub>10</sub>H<sub>11</sub>NS (see Appendix for calculation).

Accordingly the expected Fischer indole cyclization has undoubtedly taken place to produce 3-ethylthioindole, clearly illustrating that this is a feasible route to 3-alkylthioindoles.



\*J = 7 c.p.s.



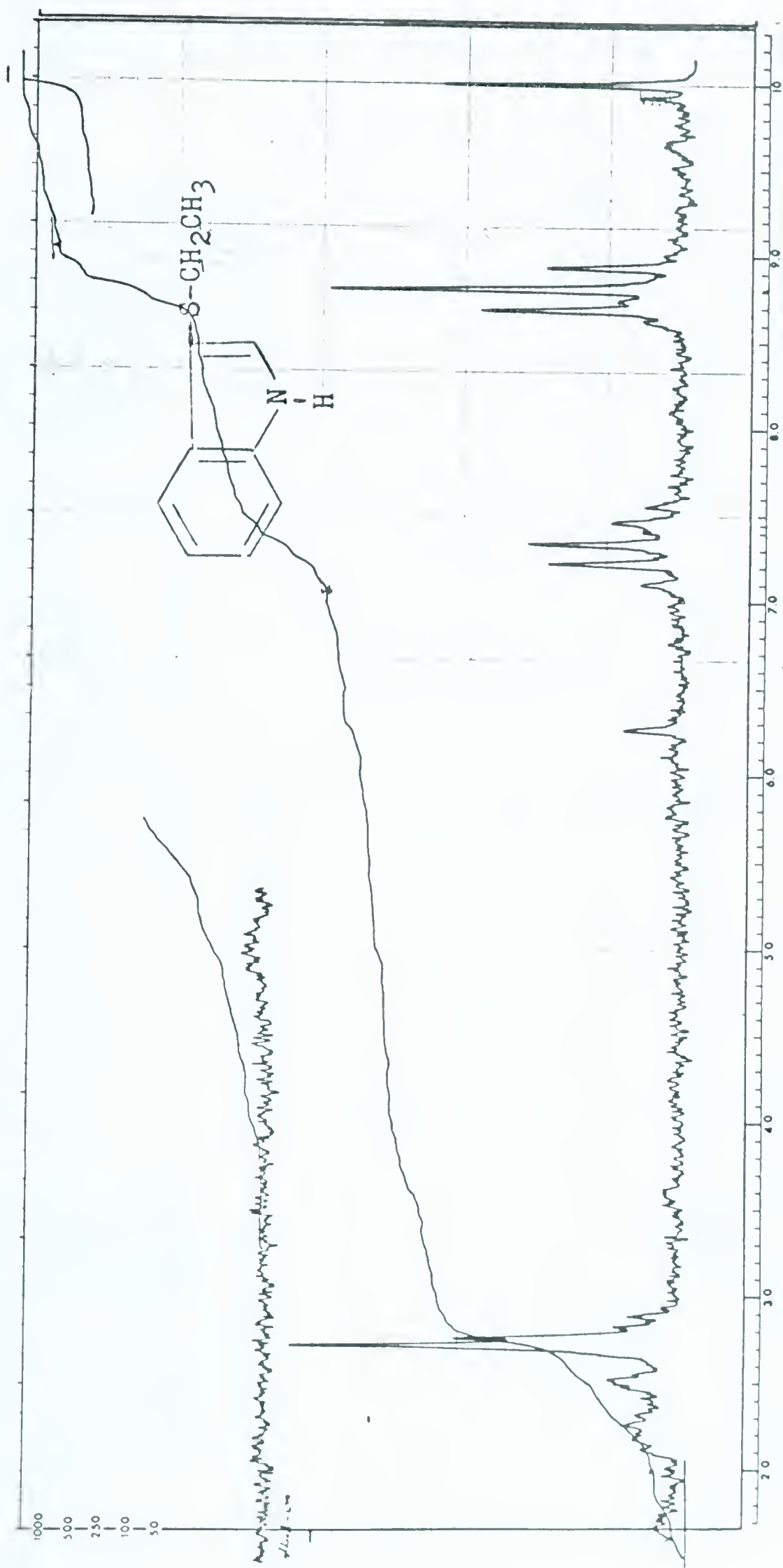


Fig. 19. N.M.R. Spectrum of 3-Ethylthioindole.

(Solvent, Deuteriochloroform. Reference - Tetramethylsilane.)



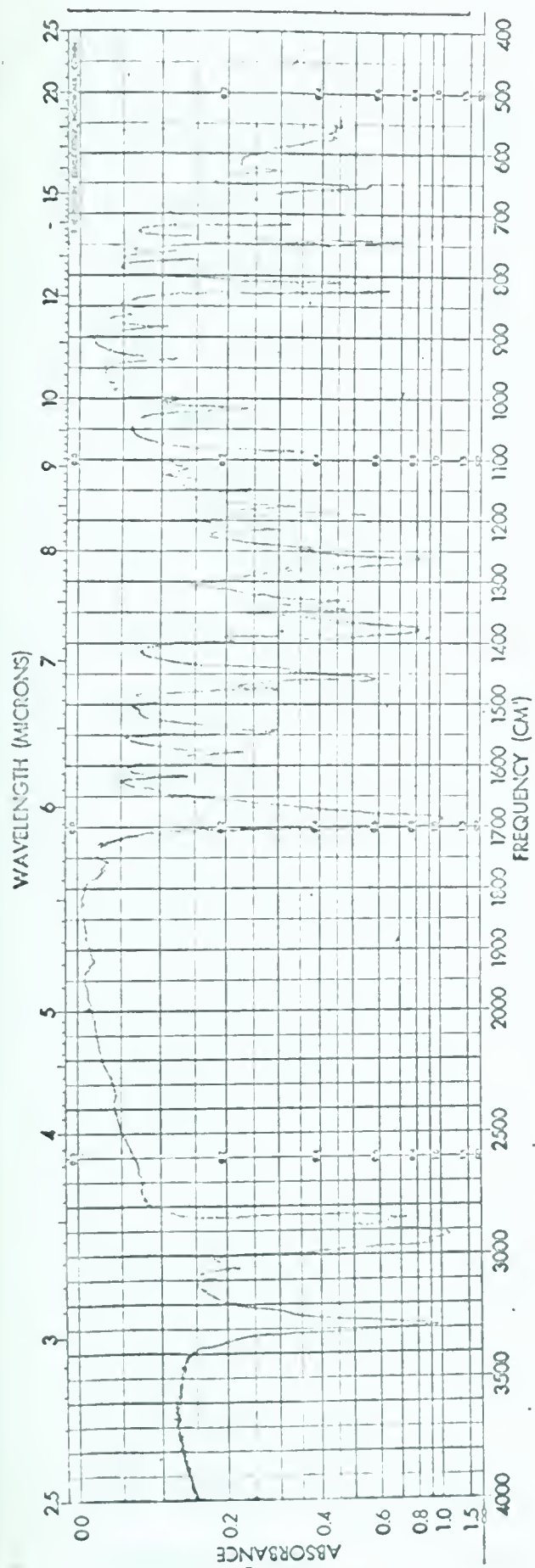


Fig. 20. I.R. Spectrum of 2-Carboxyindole-3-(p-toluenesulphonate).  
(Nujol mull).

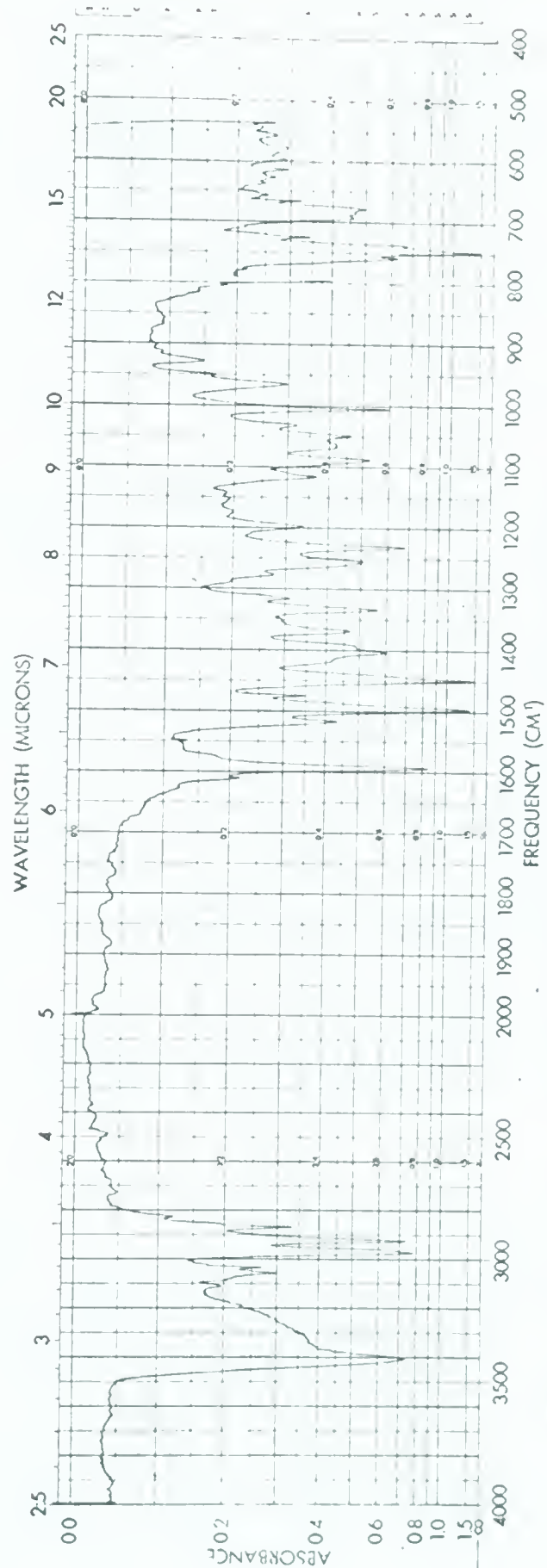


Fig. 18. I.R. Spectrum of 3-Ethylindole.  
(Neat).





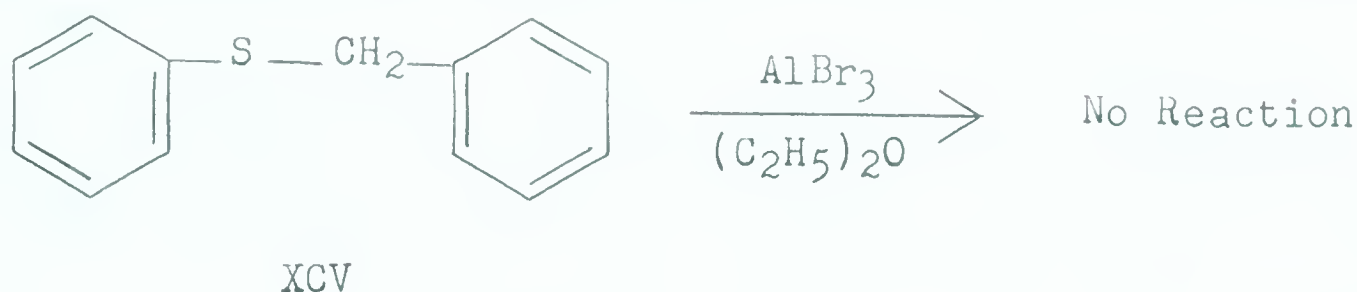
Attempts to convert 3-ethylthioindole to its N-acetyl derivative were fruitless since 3-ethylthioindole resisted acetylation by acetyl chloride in pyridine and by acetic anhydride in benzene. This behavior may not be unusual, since Madelung and Tencer (73) found that 3,3'-diindolyl sulphide is quite unreactive towards such reagents. The ethylthioindole appeared to form a picrate, on admixture with ethanol saturated with picric acid. However the picrate was a rather amorphous, ill defined compound, melting between  $\simeq -10^{\circ}\text{C.}$  and  $\simeq 0^{\circ}\text{C.}$

It is interesting to note that an attempt was made to apply this reaction sequence to the preparation of the corresponding oxygen analogue 3-ethoxyindole starting with ethoxyacetaldehyde diethyl acetal prepared by the method of Leuchs and Geiger (127). However, when ethoxyacetaldehyde diethyl acetal was subjected to a similar reaction with phenylhydrazine and boron trifluoride, a highly exothermic reaction took place yielding an intractable tar, from which no indoles could be isolated. Thin layer chromatograph (T.L.C.) gave no evidence supporting formation of 3-ethoxyindole.

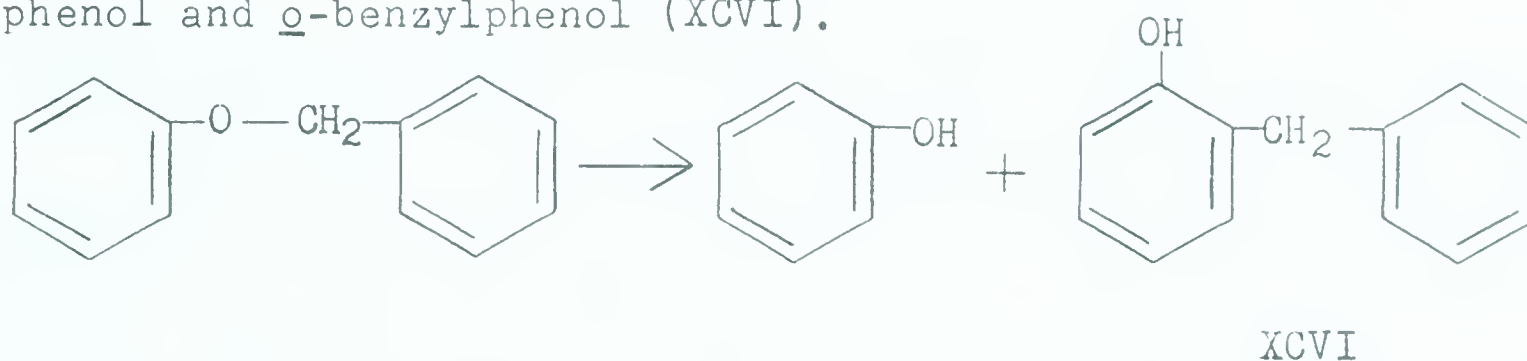
The failure to obtain 3-ethoxyindole by this route may be due to the very large difference in reactivity exhibited by oxygen and thioethers towards cleavage by acidic reagents. The relative ease of cleavage of thio and oxygen ethers has been reviewed by Tarbell and Harnish (128). Hughes and Thompson have found that thioethers are much more resistant to cleavage than are the corresponding oxygen analogues (129). Aluminium bromide in electron donor solvents was found by Harnish and Tarbell to be



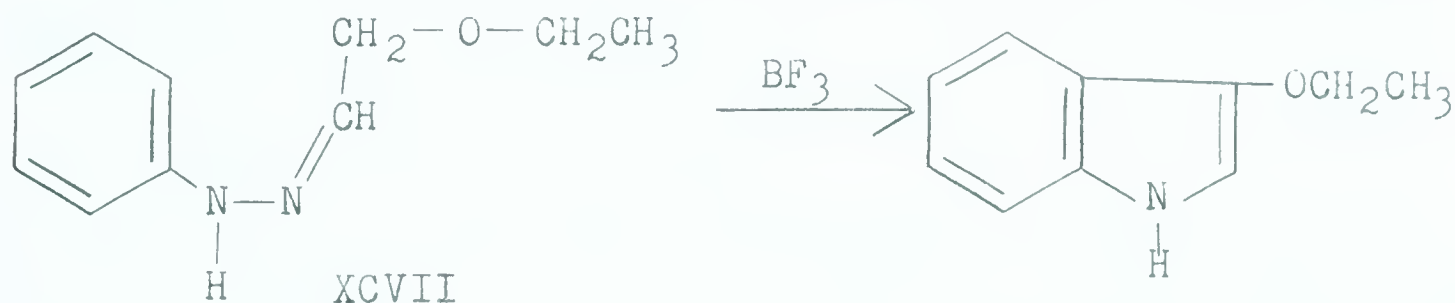
unreactive towards benzyl phenyl sulphide (XCV) (130). However



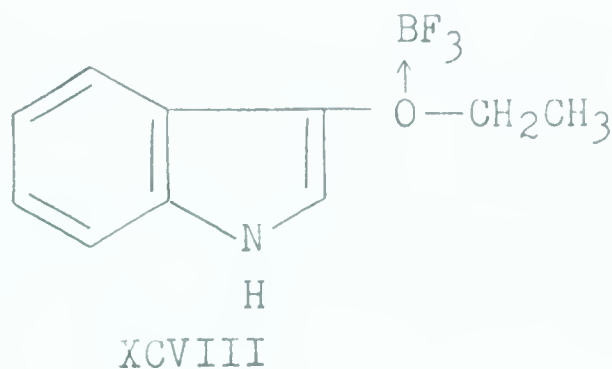
subjection of the corresponding oxygen analogue to the same conditions resulted in the cleavage of the ether link, affording phenol and o-benzylphenol (XCVI).



It is quite likely that 3-ethoxyindole actually was formed under the conditions employed in the cyclization reaction. However the Lewis acid, boron trifluoride, used to effect cyclization of the intermediate phenylhydrazone (XCVII), subsequently cleaved



the ethoxyindole by initial attack on the oxygen atom. This particular ether- $\text{BF}_3$  complex (XCVIII) should be capable of facile cleavage.

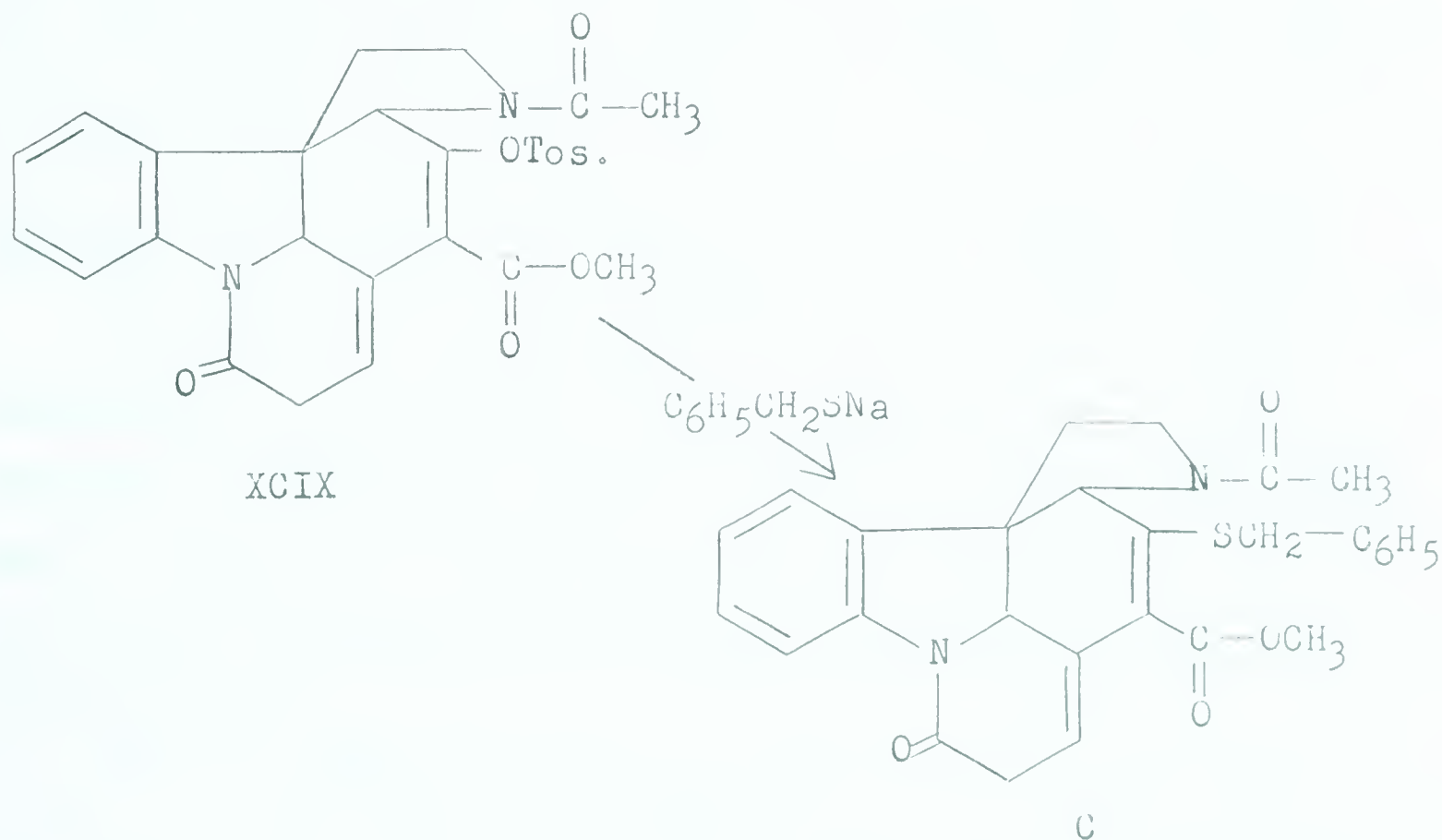




In support of this point of view it was found that 3-ethoxyindole dissolved in acetic acid and treated with boron trifluoride etherate, underwent instantaneous decomposition. A. Ettiene et al. (101) report that 3-ethoxyindole is unstable, decomposing after a week or so even when kept at 0°C.. In this laboratory 3-ethoxyindole was shown to undergo slow decomposition, even though kept under an atmosphere of nitrogen at -20°C..

(a) Synthesis Involving 2-Carbethoxyindole-3-(p-toluene sulphonate).

Information provided in the total synthesis of strychnine suggested another approach to the synthesis of indolylthioethers. Woodward et al. (132) have shown that the tosyloxyester (XCIX) undergoes facile reaction with sodium benzyl mercaptide to yield the corresponding benzylthioether (C).



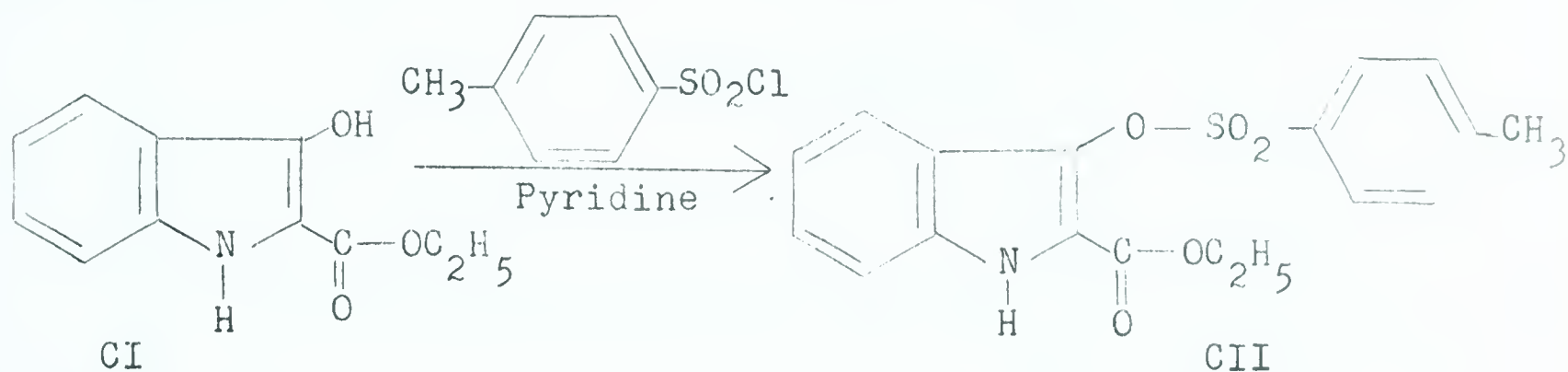
It was considered that tosylation of 2-carbethoxyindoxyl (CI) would provide a structure similar to that used in Woodward's





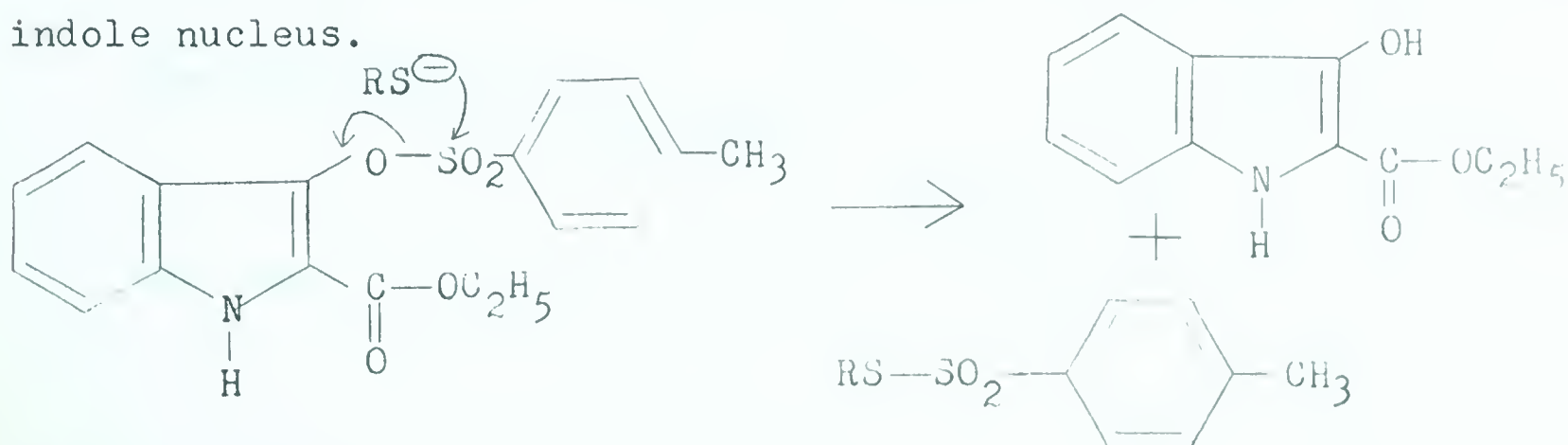
sequence. Treatment of 2-carbethoxylindoxyl with *p*-toluenesulphonyl chloride in pyridine at  $-20^{\circ}\text{C}$ . resulted in a high yield (83.4%) of 2-carbethoxyindole-3-(*p*-toluenesulphonate) (CII).

This compound melted at  $153^{\circ}\text{C}$ . and showed absorption at  $3290\text{ cm}^{-1}$



in the infrared spectrum indicative of  $\text{>N-H}$  stretching found in the indole nucleus (Fig. 20, page 84). There was no absorption in the infrared region of  $3300\text{--}3700\text{ cm}^{-1}$  due to OH. Such absorption is characteristic of the parent untosylated compound (CI) (Fig. 20a, page 92). A nuclear magnetic resonance spectrum of the compound (CII) showed a triplet at  $8.78\tau^*$  and a quartet at  $5.72\tau^*$ , characteristic of the  $-\text{CH}_2-\text{CH}_3$  group. A singlet at  $7.78\tau$  indicated the methyl group attached to the aromatic nucleus.

Treatment of 2-carbethoxyindole-3-(*p*-toluenesulphonate) with mercaptans in the presence of base in a variety of solvents, resulted in conversion of the compound back to 2-carbethoxyindoxyl. Apparently a displacement has occurred on the sulphur atom of the sulphonyl group, rather than at the position  $\text{C}_3$  of the indole nucleus.



\*J = 7 c.p.s.



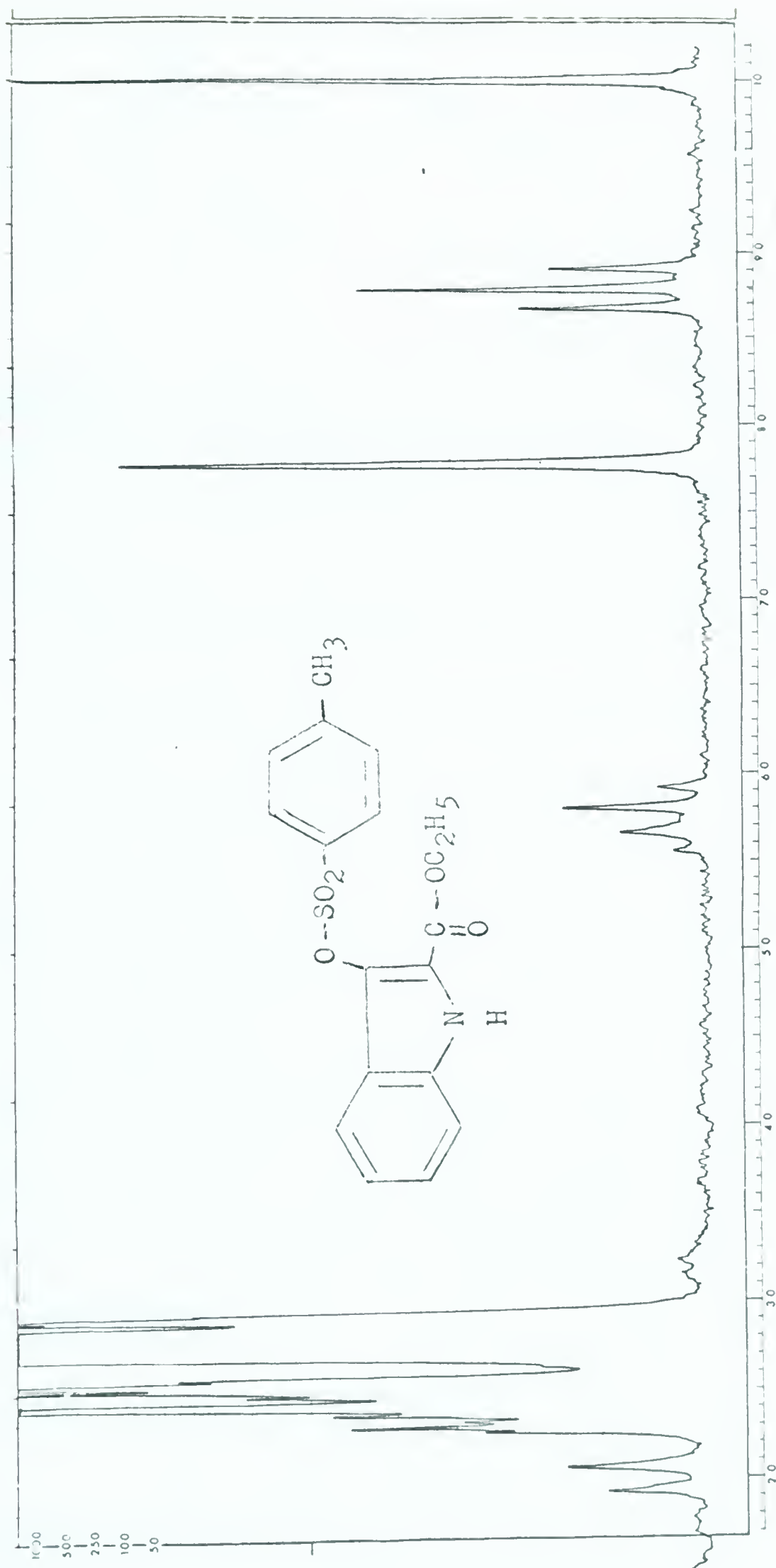
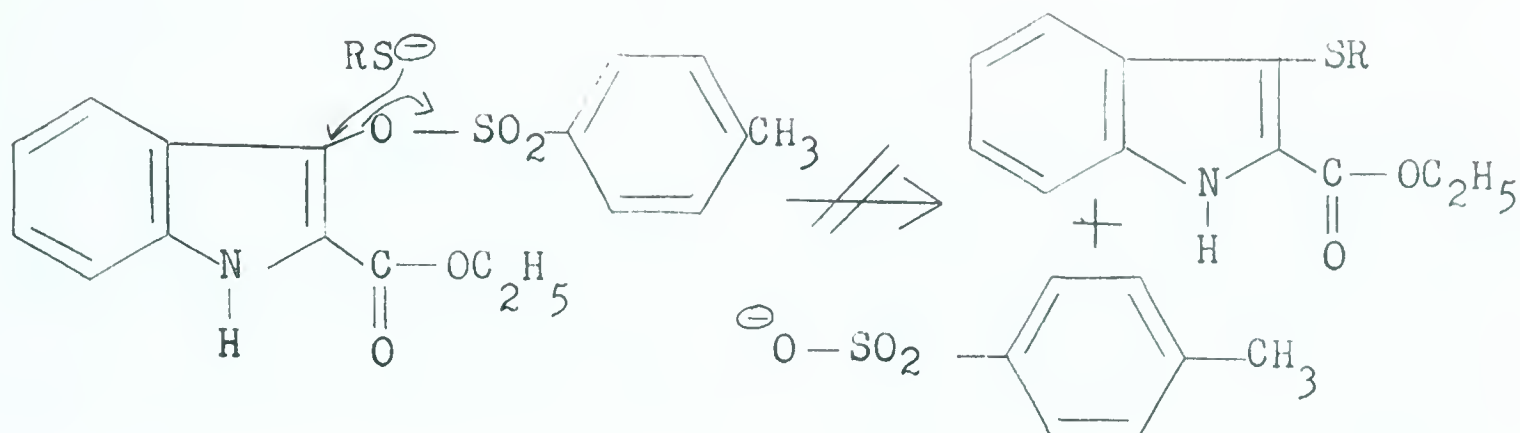


Fig. 21. N.M.R. Spectrum of Ethyl 3-(p-toluenesulphonyl)-2-indolecarboxylate.  
(Solvent, Pyridine. Reference - Tetramethylsilane.)





(b) Reactions Involving Phosphorus Pentasulphide.

Phosphorus pentasulphide has been used on occasion in the conversion of an hydroxyl group into a sulphydryl group (133) or the conversion of a keto function into a thioketone. The reaction with alcohols proceeds by the following general equation:

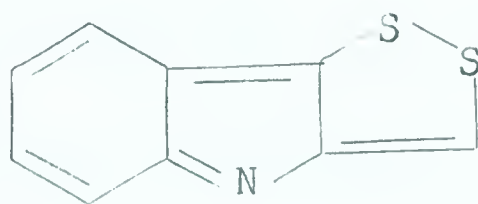


Yields are generally low. However Sugasawa (77) has reported a 70% yield in the conversion of oxindole to thiooxindole (page 25). Accordingly it was thought that the method might be useful.

Treatment of 2-carbethoxyindoxyl with phosphorus pentasulphide in boiling xylene resulted in the formation of a compound regarded as 1,2-dithiolo[4,3-b]indole-3(4H)-thione (CIV)\*, the oxidized form of 2-dithiocarboxythioindoxyl (CIII).

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\* Chemical Abstracts names the structure (CIVa) 1,2-Dithiolo-  
[4,3-b]indole.



CIVa



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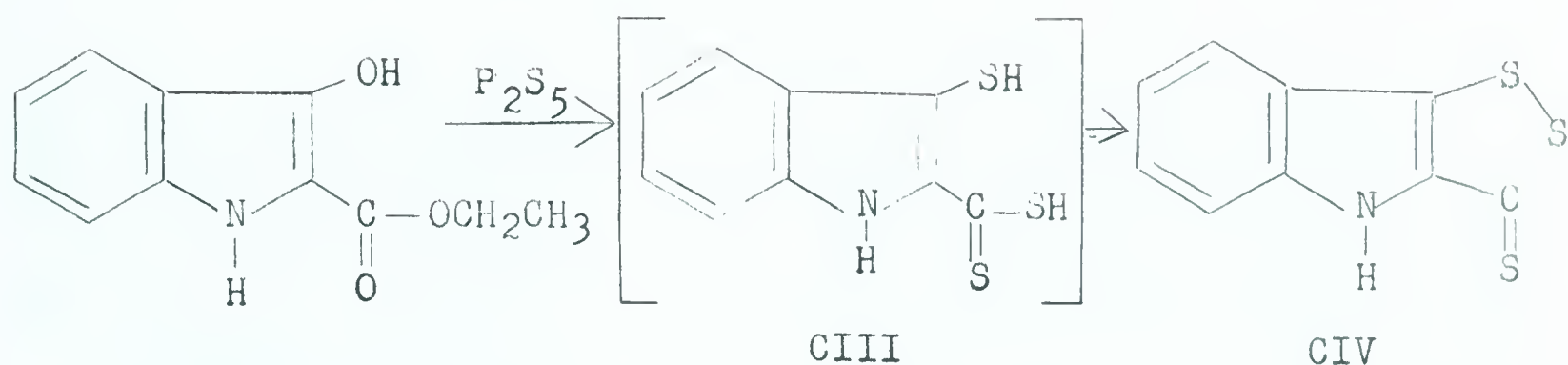
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In view of the ease with which 3,3'-diindolyl disulphide is formed from 3-mercaptoindole (76) the isolation of only the oxidized form of dithiocarboxythioindoxyl is not unusual. Elemental analysis of (CIV) is consistent with C<sub>9</sub>H<sub>5</sub>NS<sub>3</sub>. The infrared spectrum (Fig. 22, page 92) of this compound (C<sub>9</sub>H<sub>5</sub>N S<sub>3</sub>) indicated that the ester function found in the original 2-carboethoxyindoxyl had been changed as evidenced by the lack of carbonyl absorption in the region 1600-1735 cm<sup>-1</sup> (131). Absorption due to the >N—H group was observed at 3310 cm<sup>-1</sup>. No absorption bands could be clearly discerned as being due to >C=S usually found at 1050-1060 cm<sup>-1</sup> (131). Nuclear magnetic resonance spectra run in dimethylsulphoxide (Fig. 23, page 93) and in pyridine (Fig. 24, page 94) disclosed >N—H at -2.34τ and -2.29τ respectively and aromatic protons at 1.8-3.0τ (in dimethylsulphoxide). In pyridine no absorption was observed above 3.0τ.

Molecular weight determined by the cryoscopic method of K. Rast revealed a value of 231, while mass spectrometry indicated a value of 223, consistent with the empirical formula, C<sub>9</sub>H<sub>5</sub>NS<sub>3</sub> (see appendix). No reaction was observed with Ehrlich's reagent, indicating substitution at both the C<sub>2</sub> and C<sub>3</sub> positions. Raney nickel converted the compound into one whose infrared spectrum



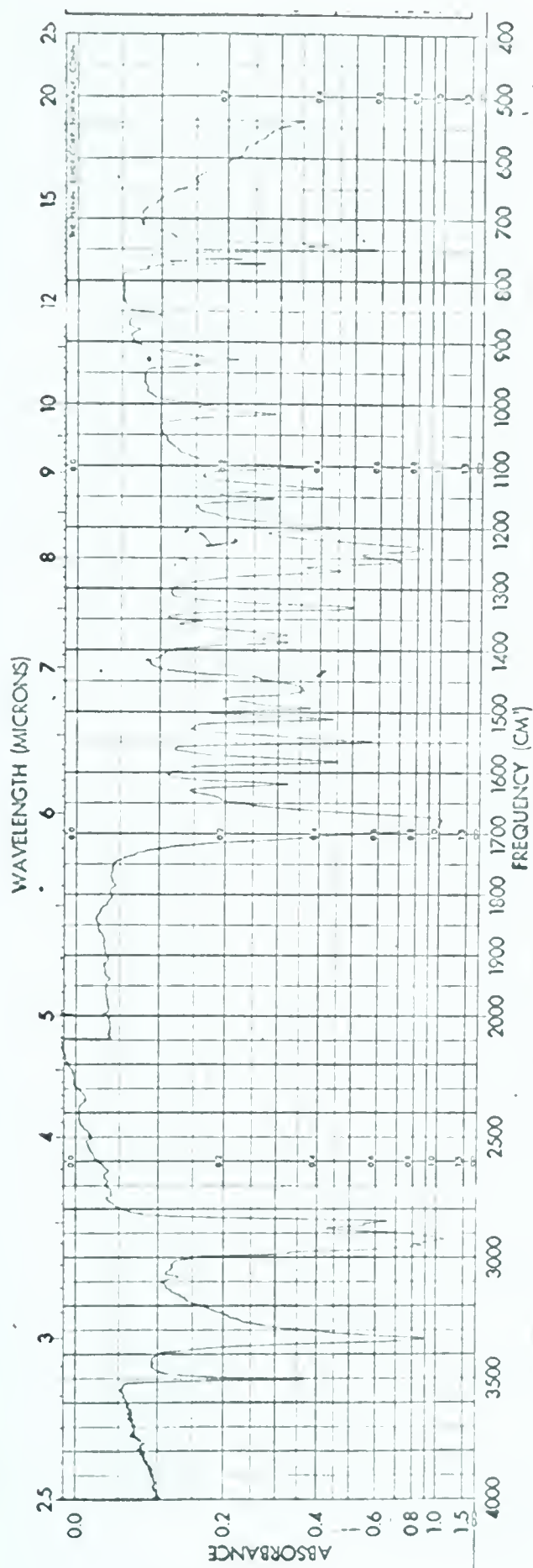


Fig. 20a. I.R. Spectrum of 2-Carbethoxyindoxyl.  
(Nujol mull).

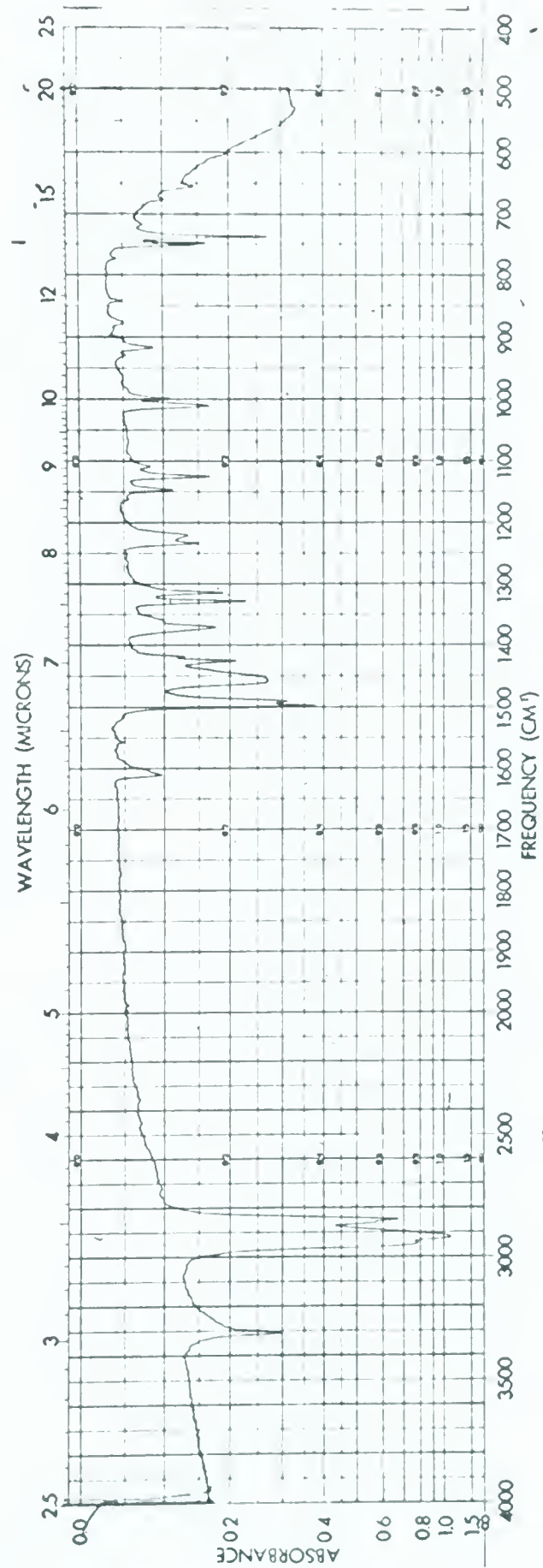


Fig. 22. I.R. Spectrum of 1,2-Dithiolo[4,3-b]indolo-3(4H)-thione.  
(Nujol mull).



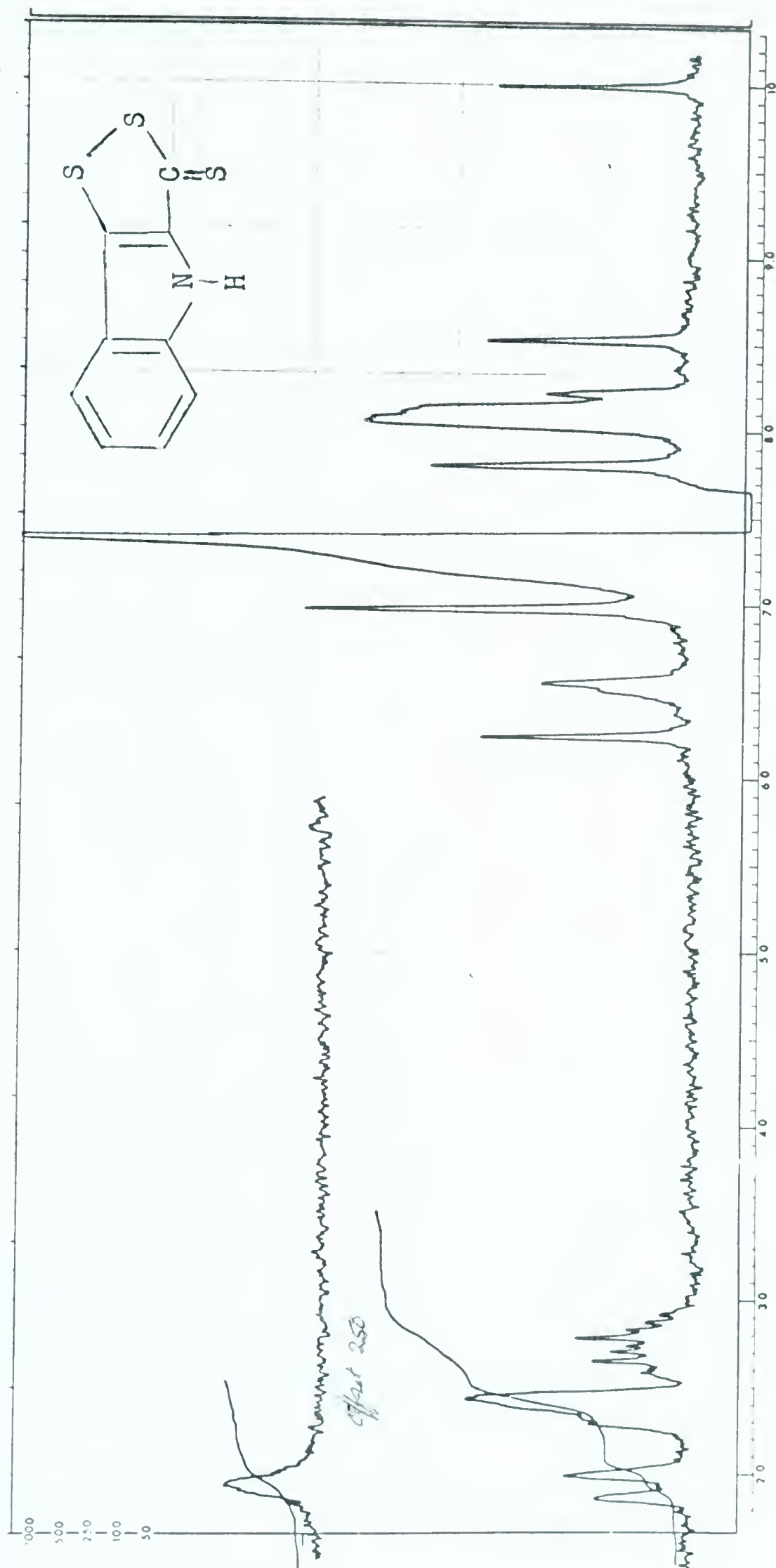


Fig. 23. N.M.R. Spectrum of 1,2-Dithiolo[4,3-b]indole-3(4H)-thione.  
(Solvent, Dimethylsulphoxide. Reference - Tetramethylsilane.)





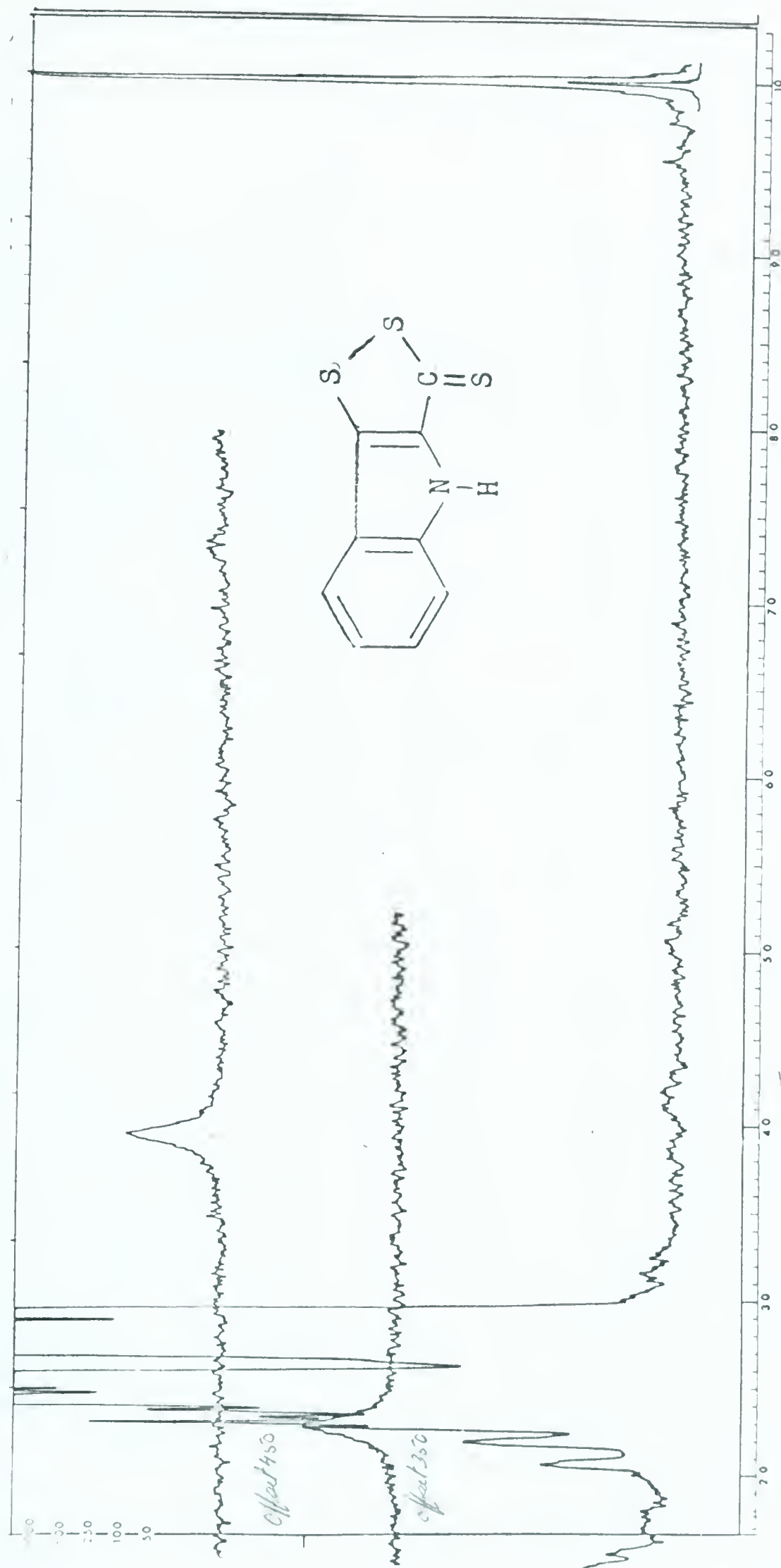


Fig. 24. N.M.R. Spectrum of 1,2-Dithiolo[4,3-b]indole-3(4H)-thione.  
(Solvent, Pyridine. Reference - Tetramethylsilane.)



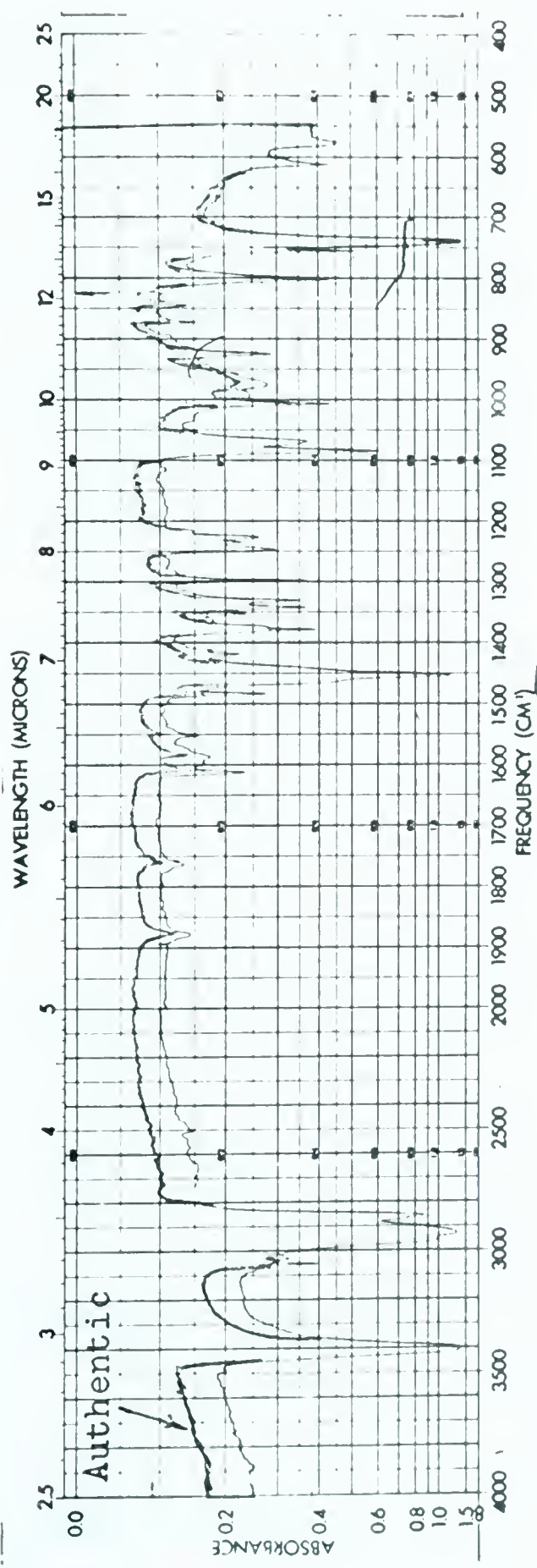


Fig. 25. Comparative I.R. Spectra of Suspected 2-Methylindole with Authentic 2-Methylindole (Nujol mull).

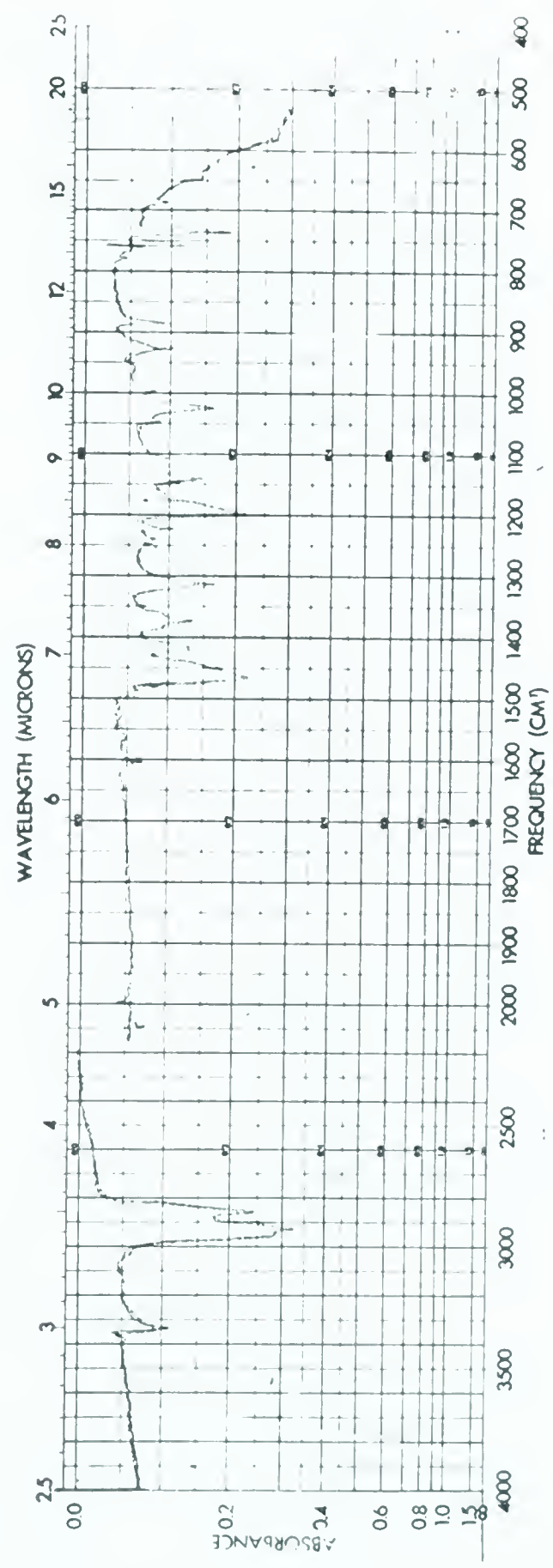
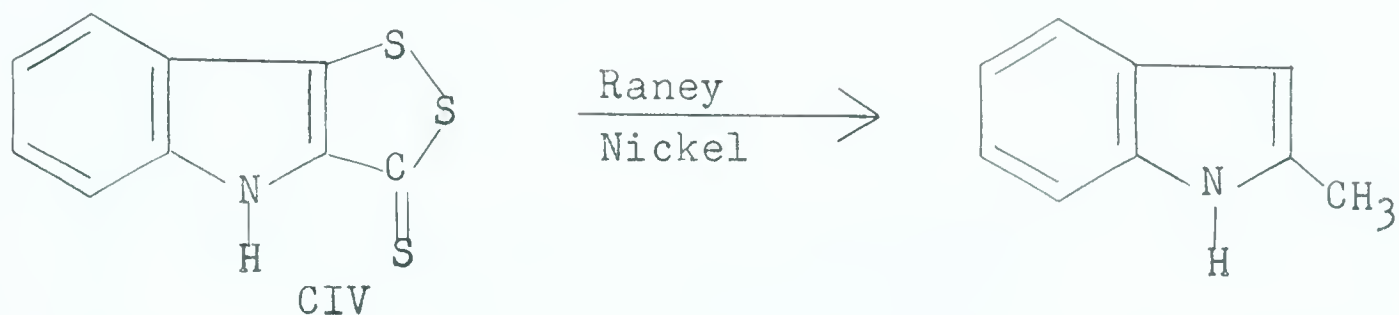


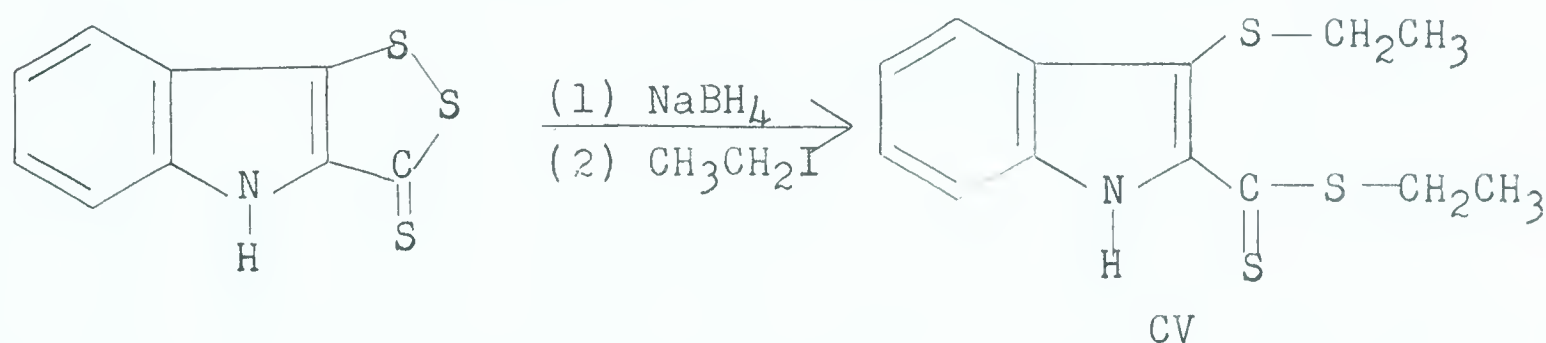
Fig. 26. I.R. Spectrum of Ethyl 3-ethylthio-2-indoledithiocarboxylate. (Nujol mull).



was almost identical to that of 2-methylindole (Fig. 25, page 95).



Treatment of 1,2-dithiolo[4,3-b]indole-3(4H)-thione with sodium borohydride in ethyl alcohol under an atmosphere of nitrogen followed by addition of ethyl iodide resulted in the formation of ethyl 3-ethylthio-2-indoledithiocarboxylate (CV).



The n.m.r. spectrum (Fig. 27, page 97) of this diethyl compound (CV) was consistent with the structure presented, showing a double set of the characteristic quartet and triplet due to the ethyl group. Infrared analysis (Fig. 26, page 95) indicated an  $\text{>N-H}$  function at  $3330 \text{ cm}^{-1}$ . The elemental analysis was also in agreement with the general formula  $\text{C}_{13}\text{H}_{15}\text{NS}_3$ .

Treatment of the dithioester (CV) with potassium hydroxide in aqueous ethyl alcohol produced  $\text{H}_2\text{S}$ , ethyl mercaptan and a compound regarded as 3-ethylthio-2-indolecarboxylic acid (CVIa)\*. The

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\*The other possibility agreeing with the I.R. spectrum is ethylthio-2-indolethiolocarboxylic acid (CVIb). An analysis (C. Daessle, Organic Micro Analysis, Montreal) agreed with neither structure. This is being repeated.





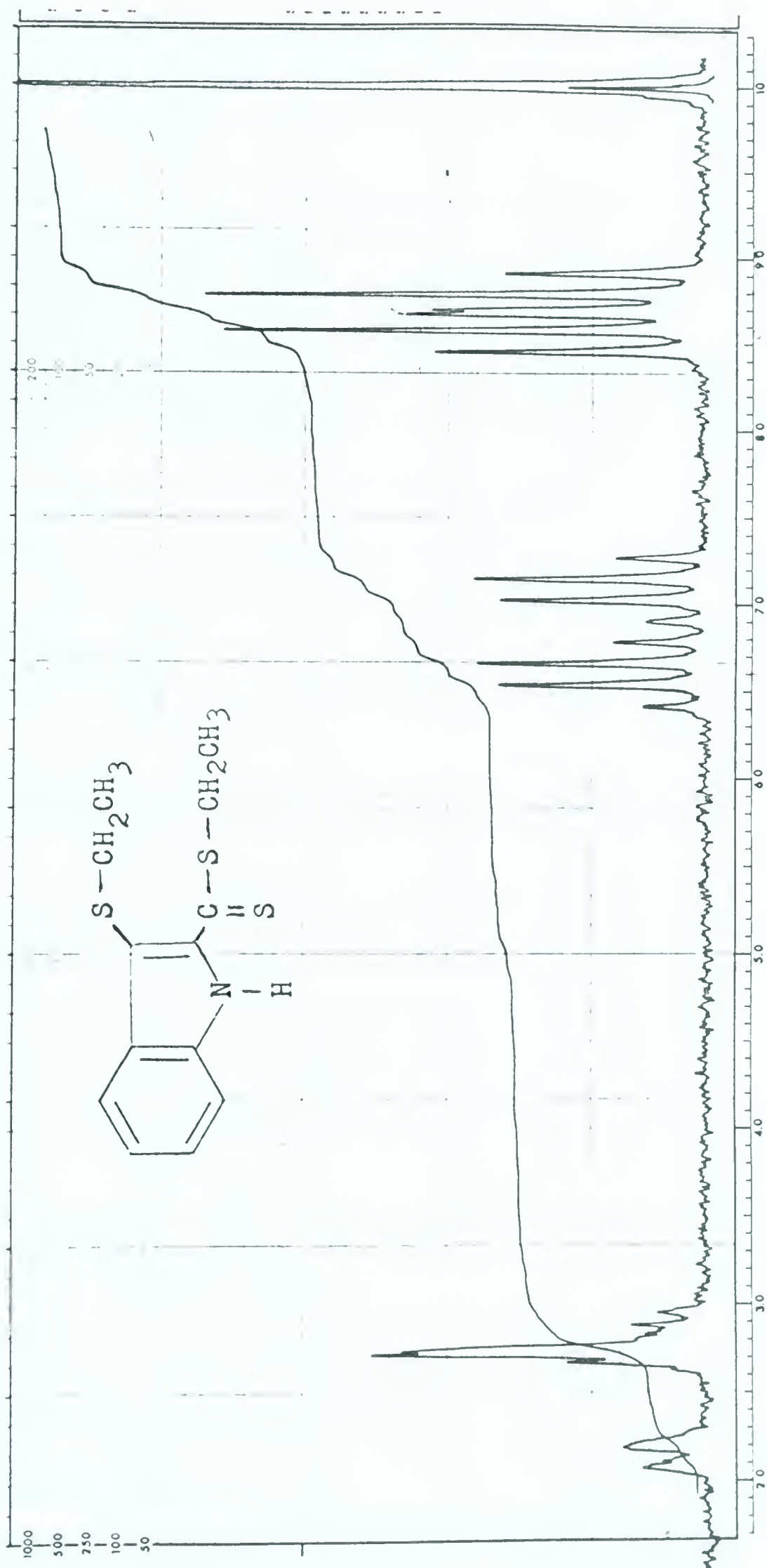
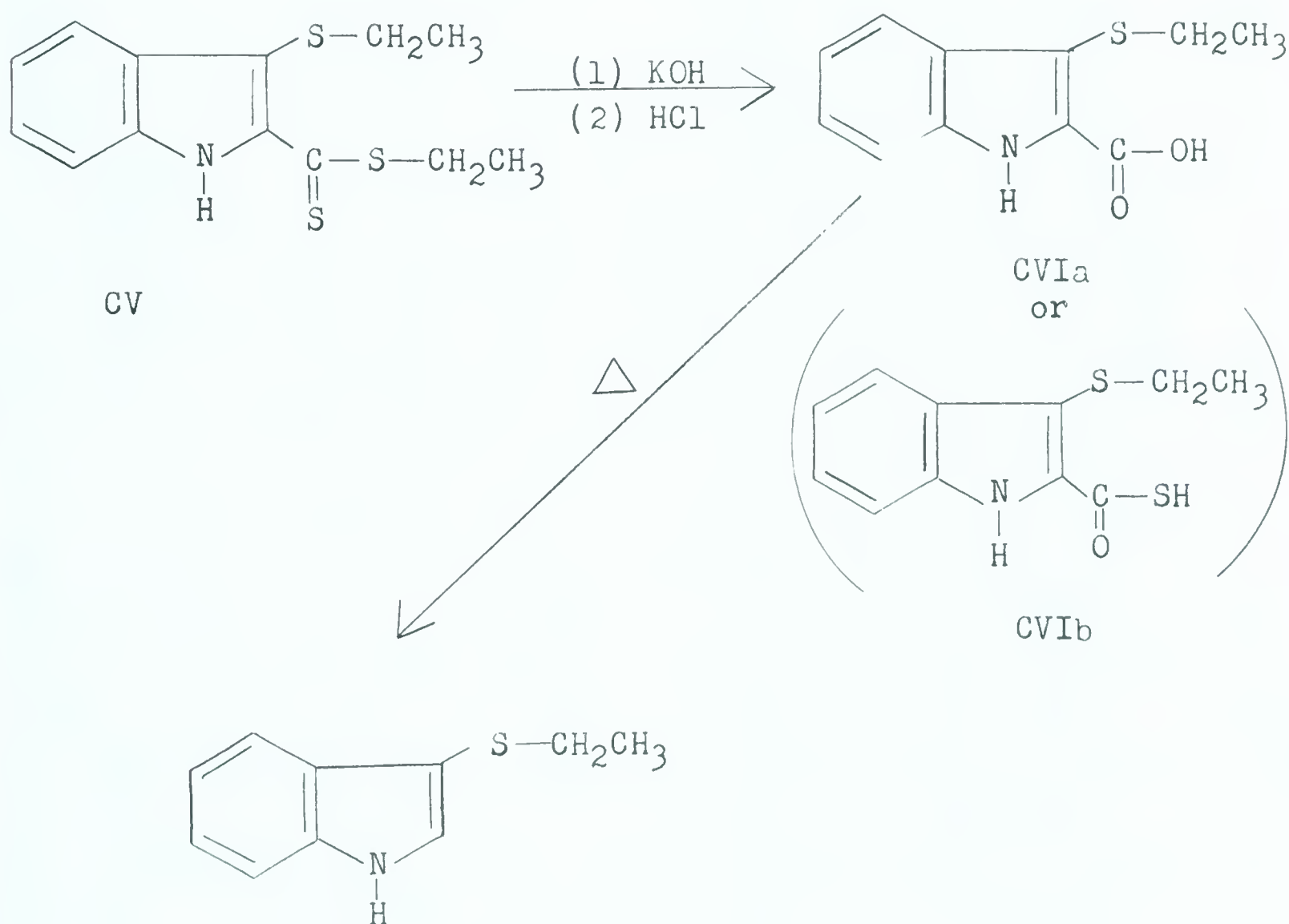


Fig. 27. N.M.R. Spectrum of Ethyl 3-ethylthio-2-indoledithiocarboxylate  
(Solvent, Deuteriochloroform. Reference - Tetramethylsilane.)



compound was soluble in base and could be precipitated on acidification. Infrared analysis revealed  $\text{>N—H}$  at  $3310\text{ cm}^{-1}$ , and carbonyl at  $1695\text{ cm}^{-1}$  (Fig. 28, page 99). Heating this compound at  $140^\circ/6\text{ mm.}$  resulted in a decarboxylation with simultaneous distillation of a compound which was found to be identical (infrared, nuclear magnetic resonance, boiling point) with 3-ethylthioindole, prepared earlier by a Fischer cyclization.



The reaction of active halogen compounds in alkaline solution with the reduced form of 1,2-dithiolo[4,3-b]indole-3(4H)-thione thus appears to be a route to the synthesis of 3-alkyl (or aryl)-



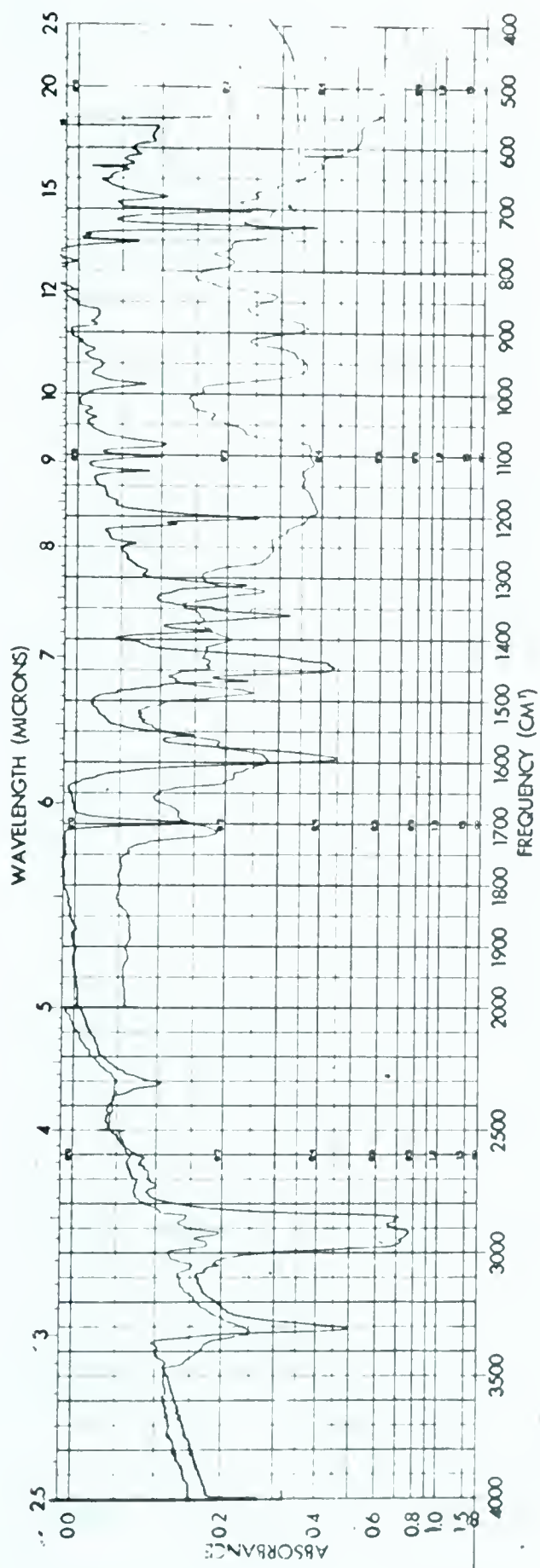


Fig. 28. I.R. Spectrum of 3-Ethylthio-2-indole Carboxylic Acid.  
(Nujol mull).

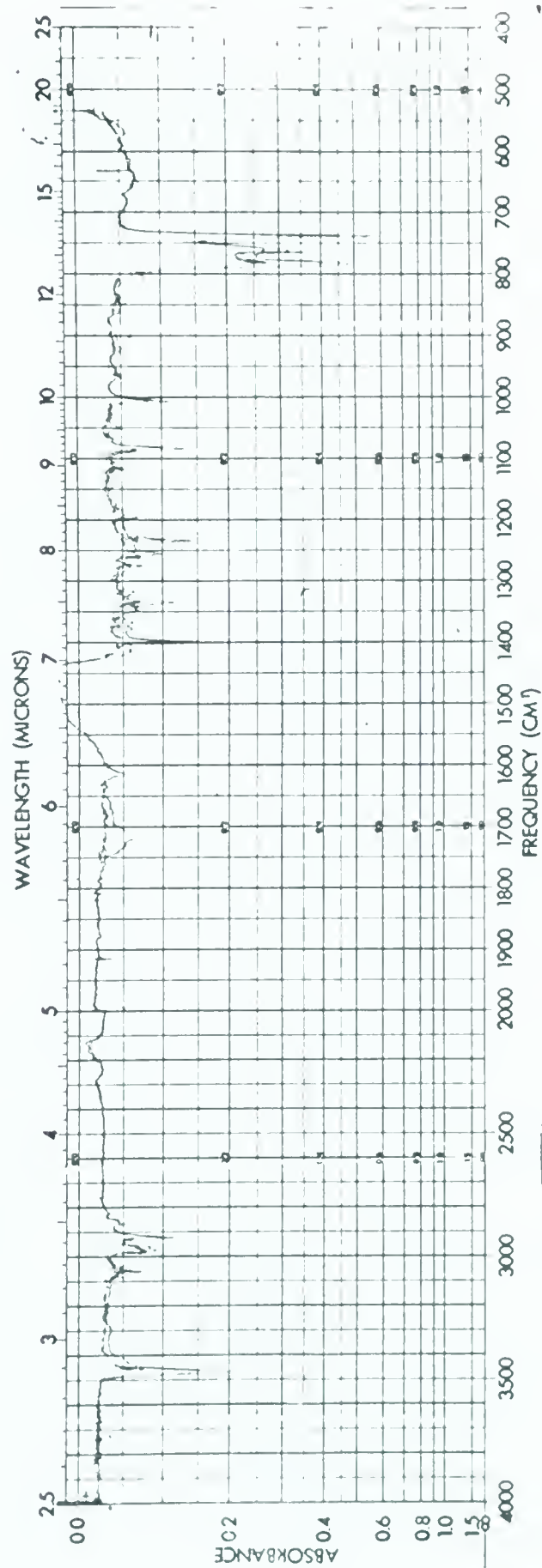
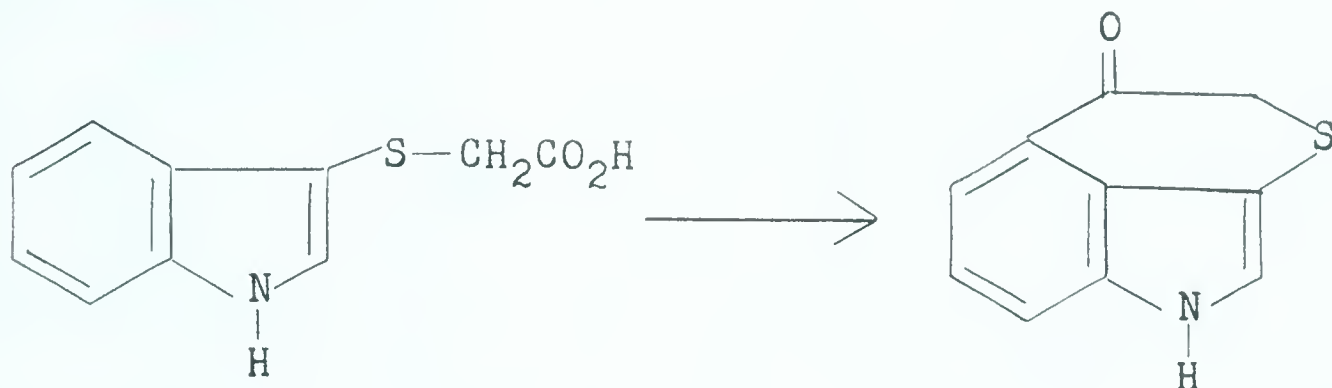


Fig. 30. Comparative I.R. Spectra of 3-Ethylthioindole.  
(Neat).





thioindoles and thus might lend itself to the preparation of 3-carboxymethylthioindole, a compound which might then be cyclized as shown below.



Accordingly 1,2-dithiolo[4,3-b]indole-3(4H)-thione was reduced with sodium borohydride in ethanol and the resulting mixture treated with ethyl bromoacetate. There was produced an orange-red compound melting at 108-110°. Infrared analysis of the compound carried out in chloroform (Fig. 34, page 101) revealed absorption at  $3390\text{ cm}^{-1}$  characteristic of the  $\text{>N-H}$  bond of indoles, and also carbonyl absorption at  $1720\text{ cm}^{-1}$ . A nuclear magnetic resonance spectrum run in  $\text{CDCl}_3$  (Fig. 29, page 102) revealed two triplets centred at  $8.71^*$  and  $8.96\tau^*$ , two singlets at  $5.78$  and  $6.46\tau$ , two quartets lying between  $5.5^*$  and  $6.3\tau^*$  along with signals at  $2.0-3.0\tau$  attributable to aromatic protons. Elemental analysis agreed with  $\text{C}_{17}\text{H}_{19}\text{O}_4\text{NS}_3$ . Molecular weight determination by the use of an osmometer revealed a value of 386.

Based on the evidence cited above, the compound (CVII) has been assigned the structure shown below: carbethoxymethyl 3-(carbethoxymethylthio)indole-2-dithiocarboxylate. This compound is expected to undergo facile hydrolysis with base, yielding a dicarboxylic acid, capable of decarboxylation to the parent acid

\*J=7 c.p.s.



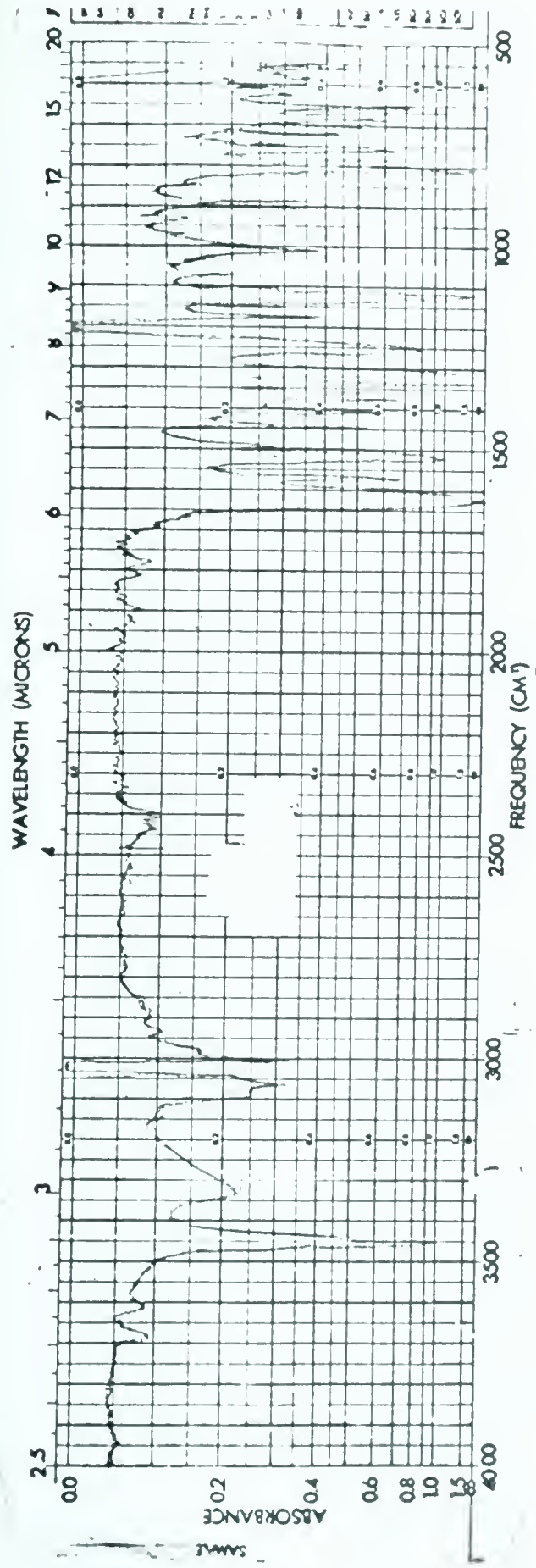


Fig. 32. I.R. Spectrum of 2-Benzoylindole.  
(Solvent, Chloroform).

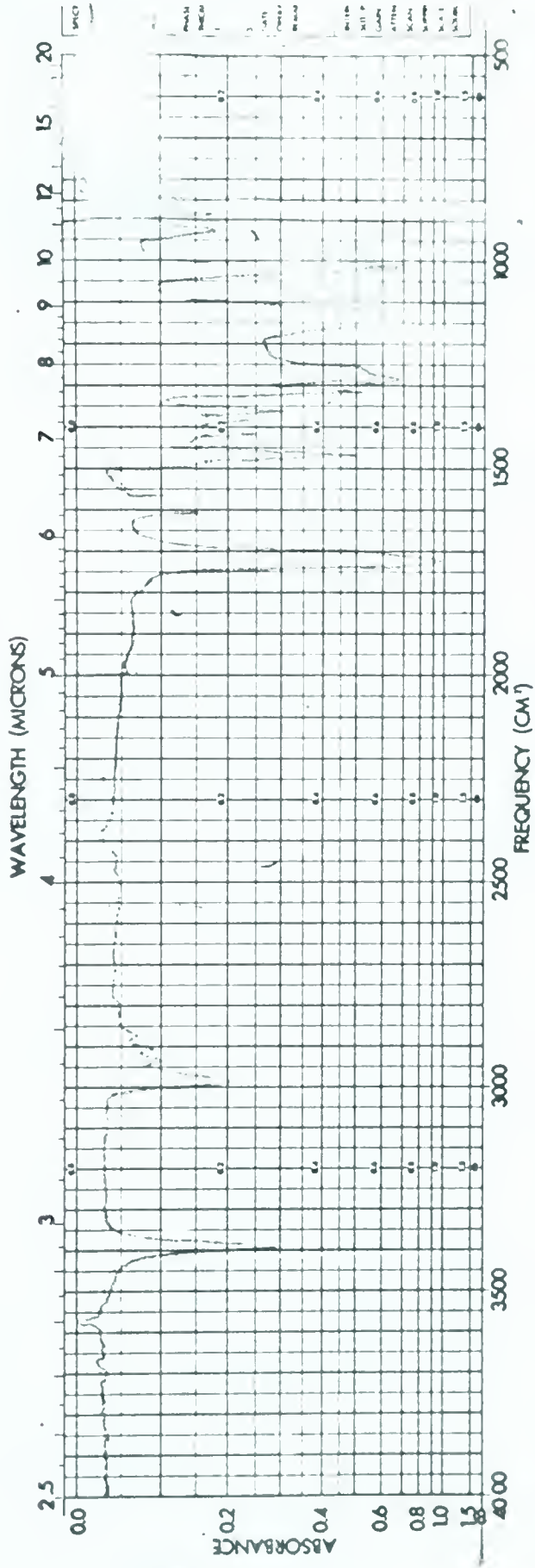


Fig. 34. I.R. Spectrum of Carbethoxymethyl 3-(carbethoxymethylthio)-  
2-indoledithiocarboxylate.  
(Solvent, Chloroform).



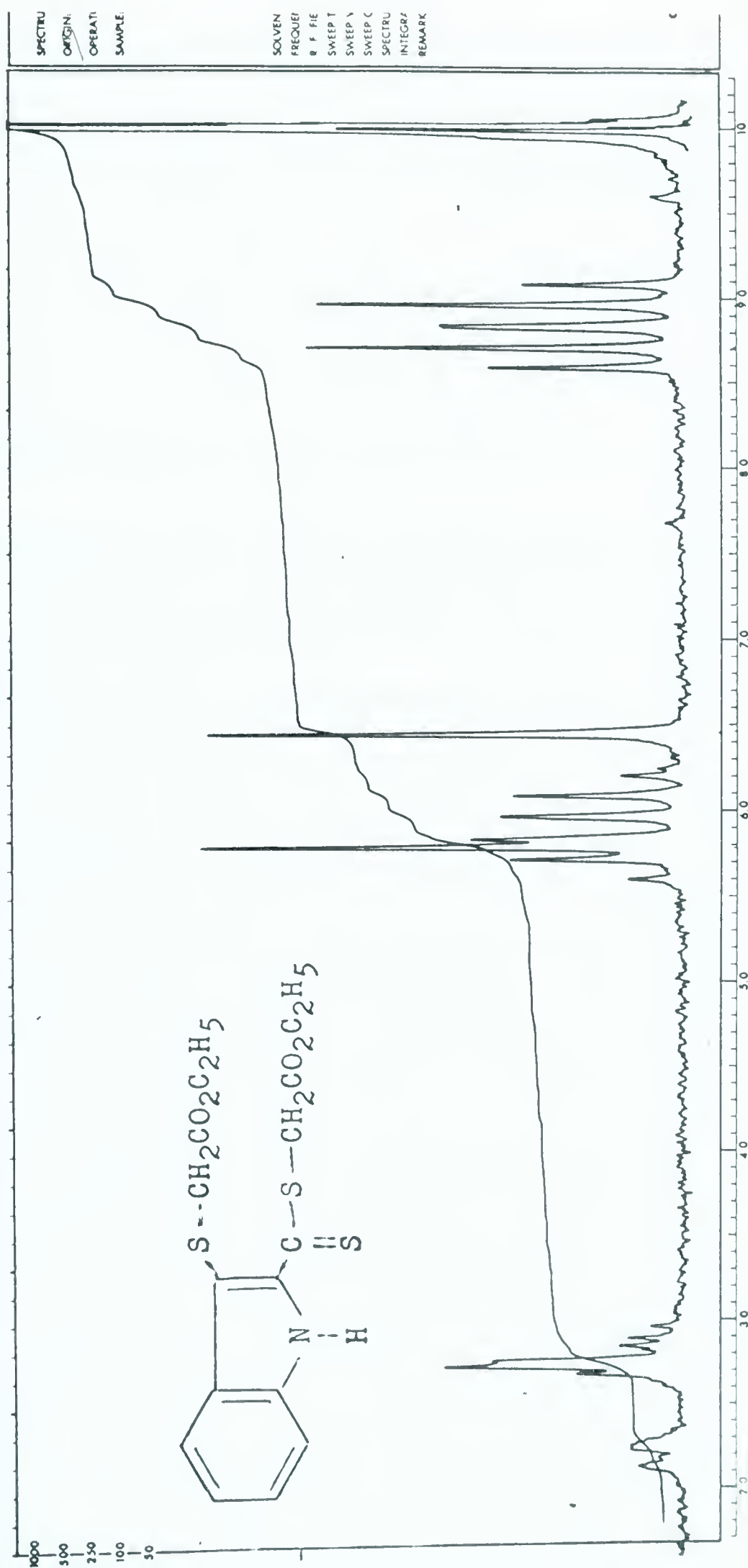


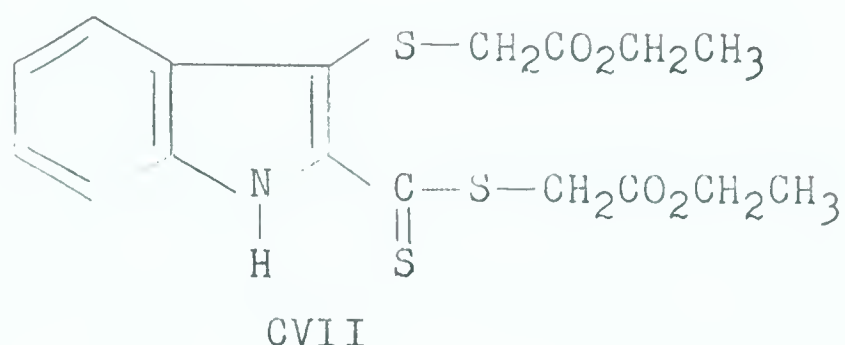
Fig. 29. N.M.R. Spectrum of Carbethoxymethyl 3-(carbethoxymethylthio)indole-2-dithiocarboxylate.

(Solvent, Deuteriochloroform. Reference - Tetramethylsilane.)









of the originally required compound.

Determination of 2- or 3- Substitution in the Indole Nucleus.

In the reaction between N-benzoyl-3-bromoindole and ethyl mercaptan in the presence of potassium carbonate, a substance was isolated which was identical to the compound first isolated by Madelung and Tencer (73) and described by them as being probably 3,3'-diindolyl sulphide. The peculiar properties cast some doubt upon the correct assignment of structure. It was felt necessary that this structure be unequivocally established before attempts could be made to investigate its mode of formation. This required a method which could be used to determine whether the indole nucleus was substituted at the C<sub>2</sub> or C<sub>3</sub> position. It has been discovered that the  $\text{>N-H}$  proton of indole couples not only with the proton of the C<sub>2</sub> position, but also undergoes approximately equal long range coupling with the C<sub>3</sub> proton (134). It is, therefore, not possible to assign the position of substitution by observation of decoupling when one converts the  $\text{>N-H}$  of indole to  $\text{>N-D}$ .

Witkop et al. (121) have shown that nuclear magnetic resonance can be used to determine substitution at the C<sub>2</sub> or C<sub>3</sub> position of



the indole nucleus. In carbon tetrachloride or deuterochloroform solution, the signal for the  $C_2$  proton of indole, N-methylindole, skatole and tryptamine was at the respective  $\tau$  value (referred to the internal standard, tetramethylsilane) of 3.32 (triplet), 3.18 (doublet), 3.20 (poorly resolved doublet), and 3.08 (doublet).

The  $C_3$  proton signal of indole, N-methylindole and 2-methylindole was at a  $\tau$  value of 3.62 (triplet), 3.52 (doublet), and 3.87 (broad single peak) respectively. Thus the  $C_3$  proton gave a signal at higher field than that found for the  $C_2$  proton, the difference in chemical shift for these two protons lying between 0.3 and 0.8  $\tau$  units. The signals for the  $C_2$  and  $C_3$  protons were quite clearly discernable, well separated, and at higher field than those for the remaining protons in the indole nucleus, except for the case of quebrachamine, whose signal for the  $C_2$  proton was buried in the more complicated absorption due to the aromatic ring protons in the region approximately between 2 and 3  $\tau$ .

When groups more electronegative than alkyl substituents were introduced into the 2- position, the signal for the remaining  $C_3$  proton, normally found well isolated at about 3.5 to 3.9  $\tau$  (121), occurred considerably farther downfield, at approximately 2.8 to 3.2  $\tau$ , in the region where the  $C_2$  proton absorption is shown to occur in indole and 3-alkylated indoles (3.08-3.32  $\tau$ ). Hence observation of a signal in this region is not conclusive proof that the 3-, rather than the 2-, position has been substituted.

Among the factors listed by Roberts (135) which affect the extent of chemical shift of protons is that due to solvent. It occurred to us that, because of the obvious difference in electron



environment at the 2- and 3- protons, change in solvent from one of non-polar character to one of highly polar character might affect one of the protons ( $C_2$  or  $C_3$ ) to a greater extent than it did the other. Hence solvent shift or lack of solvent shift might be used as a means to determine whether we were dealing with a 2- or 3- substituted indole nucleus.

Accordingly a number of indole derivatives were synthesized in which substitution at the 2 or 3 position was known. These, along with indole itself, were subjected to n.m.r. analyses on a 60 megacycle Varian Spectrometer using a variety of solvents. Tetramethylsilane was used as an internal standard and all values were expressed on the  $\tau$  scale (136). To aid in determining the position of the  $C_2$  or  $C_3$  proton resonance signals, use was made of the fact that the doublet or multiplet, caused by spin-spin coupling between the proton on the nitrogen atom and the  $C_2$  or  $C_3$  proton, collapses to a singlet or to a simpler system when the  $>N-H$  is converted to  $>N-D$  (121). Where the complexity of signals for the aromatic protons interfered, the greater resolving power of the 100 Megacycle Varian Spectrometer (HR-100) was found to be helpful in locating  $C_2$  or  $C_3$  proton resonance signals. The results of the analyses are shown in Table III, page 111.

The signal for the  $C_3$  proton in either indole or 2-methylindole is quite well discernible in all of the seven solvents employed. Its position, ranging from  $3.52\tau$  to  $3.71\tau$  ( $\Delta\tau = 0.19$ ) for indole and  $3.86\tau$  to  $4.10\tau$  ( $\Delta\tau = 0.24$ ) for 2-methylindole, lies well beyond and at higher field than the absorption peaks of the aromatic protons ( $2.0\tau$  to  $3.0\tau$ ). There is a slight downfield







TABLE II \*

The effect of solvent on the position of the resonance signal for the proton on the nitrogen atom of indole and substituted indoles

	Position of the signal for the N—H proton in the solvents ( $\tau$ )						
	CCl <sub>4</sub>	CDCl <sub>3</sub>	Acetone	Dimethyl sulphoxide	Dioxane	CS <sub>2</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> N
Indole	(3.0)	(2.9)	0.00	-1.01	+0.48	(3.1)	-0.08
2-Methylindole	(3.1)	(3.0)	+0.33	-0.82	+0.84	(3.1)	+0.08
3-Methylindole	(3.1)	(2.9)	+0.48	-0.69	+0.91	(3.1)	-0.59
Ethyl indole-2-carboxylate	Insol.	+0.44	-0.79	-1.87	-0.51	Insol.	?
3-Bromoindole	Insol.	(2.8)	-0.61	-1.46	+0.22	(2.9)	-1.01
$\beta,\beta'$ -Diindolylsulphide	Insol.	Insol.	-0.46	-1.54	+0.13	Insol.	Insol.
3-Benzoylindole	Insol.	Insol.	Insol.	-2.00	Insol.	Insol.	Insol.
2-Benzoylindole	Insol.	+0.08	-1.06	?	?	?	?
3-Acetylindole	Insol.	Insol.	Insol.	-1.92	Insol.	Insol.	Insol.
3-Acetyl-2-methylindole	—	—	—	-1.8	—	—	—

NOTE: Figures in parentheses are approximate locations of the signals. The term "insol." means that the compound was either insoluble or insufficiently soluble for satisfactory n.m.r. analysis. A question mark indicates that the signal for the N—H proton could not be detected.



shift of the signal in polar solvents as compared to its position in non-polar solvents.

The signal for the  $C_2$  proton of indole is found between 2.70 and 3.46 $\tau$ , a range ( $\Delta\tau$ ) of 0.76 $\tau$  units, whereas for 3-methylindole the signal is found between 2.94 and 3.65 $\tau$ , over a range ( $\Delta\tau$ ) of 0.71 $\tau$  units.

It is clearly seen that the signal position of the  $C_2$  proton in the indole nucleus is influenced to a much greater extent by the nature of the solvent than is that of the  $C_3$  proton. In more polar or more basic solvents, the chemical shift of the  $C_2$  proton is sufficient to place it in the region assigned to the aromatic proton absorption. In some solvents (acetone, dimethylsulphoxide, dioxan, and triethylamine) the assignment of the signal for the  $C_2$  proton of indole was not certain and hence is tentative, as indicated by the values in parentheses in Table III. However, from the simplification of multiplets caused by the conversion of  $\geq N-H$  to  $\geq N-D$ , and with the aid of high-resolution spectra, it was quite definitely ascertained that the  $C_2$  proton signal must be below certain  $\tau$  values as indicated in Table III. In only one solvent, acetone, was similar ambiguity found for the signal position of the 2 proton in 3-methylindole.

It is of interest to note that the methyl group in both 2- and 3-methylindole caused greater shielding of the  $C_3$  and  $C_2$  protons than that found for indole itself, as indicated by the shift to higher field of the signals for these protons in the alkylated indoles. This is apparent in both cases only when one compares the spectra obtained in the same solvent. Witkop et al



(121) have noted the greater shielding effect on the  $C_3$  proton in 2-methylindole caused by the introduction of the methyl substituent, but their data indicate that a similar increased shielding of the  $C_2$  proton is not found in 3-methylindole. In fact the  $C_2$  proton in 3-methylindole was found to give a signal at 3.20 $\tau$  while the  $C_2$  proton of indole absorbed at 3.32 $\tau$ . However, their use of  $CCl_4$  as solvent for indole but  $CDCl_3$  for the methylindole accounts for this inconsistency. From our observations it is now clear that the more polar solvent,  $CDCl_3$ , will cause a significantly greater decrease in shielding for the  $C_2$  proton than for the  $C_3$  proton in indole and any increase in shielding due to the methyl substituent is not sufficient to compensate for the large downfield shift of the  $C_2$  proton signal due to the solvent effect.

Substitution of the  $C_2$  or  $C_3$  proton of indole by an electron-withdrawing group such as acetyl, carbonyl, carbethoxy, and benzoyl shifts the absorption of the remaining  $C_3$  or  $C_2$  proton as much as 0.7 to 1.2 $\tau$  units downfield from the corresponding position of the signals of indole itself. Here again one must compare spectra of compounds in the same solvent. A greater shift occurs for the  $C_2$  than for the  $C_3$  proton: the  $\Delta\tau$  ranges from 0.95 to 1.2 for the  $C_2$  proton as compared with 0.7 to 1.1 for the  $C_3$  proton. Thus, for ethyl indole-3-carboxylate, the  $C_2$  proton signal in  $CDCl_3$  is a doublet at 2.18 $\tau$ ,  $J=3$  c.p.s., while that of the  $C_3$  proton in 3-methylindole and indole in the same solvent occurs at 3.39 $\tau$ <sup>\*</sup> and 3.26 $\tau$ <sup>\*\*</sup> respectively. On the other hand, for ethyl indole-2-carboxylate, the  $C_3$  proton signal is found at 2.80 $\tau$ <sup>†</sup> in dioxan solution while in the same solvent, the  $C_3$  proton signal for 2-methylindole

\*  $J=1$  c.p.s.      \*\*  $J=3$  c.p.s.

†  $J=1$  c.p.s.







and indole is at  $3.88\tau^*$  and  $3.52\tau^{**}$  respectively.

For compounds in which the  $C_3$  proton was replaced by either sulphur or halogen, the deshielding effect on the  $C_2$  proton due to these substituents was less than that found for the carbonyl compounds.

In dimethylsulphoxide, for the two compounds ethyl indole-3-carboxylate and 3-acetylintole it was noted that the normally expected doublet for the  $C_2$  proton, due to spin-spin coupling with the proton on the adjacent nitrogen atom, did not occur. Instead, a sharply defined singlet was observed at  $1.88\tau$  and  $1.66\tau$  respectively. Deuteration produced an unchanged singlet at the same position. The carboxylate exhibited the same phenomenon in triethylamine. The insolubility of the 3-acetylintole in triethylamine thwarted attempts to detect a similar observation. In other solvents (e.g. acetone and dioxan) doublets due to spin-spin coupling were clearly shown. When the spectral grade acetone solvent was treated with a small amount of water or dilute hydrochloric acid, 3-acetylintole still showed a doublet, unchanged, for the  $C_2$  proton. In reagent pyridine the spectrum of 3-acetylintole gave a closely spaced doublet at  $1.75\tau$  which collapsed to a singlet when the compound was deuterated.

We have assigned the  $C_2$  proton absorption of 3-acetylintole to the doublet appearing at  $1.81\tau$ ,  $J=1.5$  c.p.s. on the basis of the collapse of this doublet to a singlet in the N-deuterated compound. Additional evidence to support the assignment was obtained from the fact that this signal disappeared completely when the  $C_2$  hydrogen was substituted by a methyl group.

\*  $J=2$  c.p.s.

\*\*  $J=1$  c.p.s.



From the data in Table III, page 111, it is clear that the greater solvent dependence of the chemical shift of the  $C_2$  proton as compared with that of the  $C_3$  proton is a useful means of determining or corroborating 2- or 3- substitution in the indole nucleus. The limited solubility or insolubility of the compounds in some of the solvents normally employed for n.m.r. spectra determinations restricts the utility somewhat. However, considering a pair of solvents such as acetone and dimethylsulphoxide, in which most of the compounds are soluble, the position of the  $C_3$  proton signal is nearly the same in either solvent, with a maximum difference of 0.03 $\tau$ . But for the  $C_2$  proton, a difference in signal position of 0.08 to 0.17 $\tau$  occurs. A larger difference in the chemical shift for the  $C_2$  proton is found when one compares signal positions in a non-polar or slightly polar solvent ( $CDCl_3$ ) and highly polar solvent (acetone or dimethylsulphoxide).

It is of interest to note that the signal position for the proton attached to the nitrogen atom of the indole ring is influenced even more strongly by the solvent employed than is the  $C_2$  proton. Table II, page 106, summarizes the information obtained. Where the signals are clearly discernible, they are found generally to be broad, but less so in dimethylsulphoxide.

In non-polar, or relatively non-polar solvents ( $CCl_4$ ,  $CDCl_3$ ,  $CS_2$ ), the  $>N-H$  signals of indoles and alkylated indoles are buried in the complex absorption due to the aromatic protons, roughly in the region 2.9 to 3.1 $\tau$ . Approximate locations of the signal are given by the figures in parentheses, and are obtained from the decrease in integrated areas for the N-deuterated com-





TABLE III\*  
The effect of change of solvent on the position of the resonance signals for the  $\alpha$  or  $\beta$  protons in  $\beta$ - or  $\alpha$ -substituted indoles

Compound	Position of the signals for the $\alpha$ and $\beta$ protons in the solvents ( $\tau$ )							Overall $\Delta\tau$
	CCl <sub>4</sub>	CDCl <sub>3</sub>	Acetone	Dimethyl sulphoxide	Dioxane	CS <sub>2</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> N	
Indole <sup>1</sup> ( $\alpha$ proton)	3.46 a	3.26 a	<2.75 (2.72 b*)	<2.71 (2.6 to 2.7)	<2.89 (2.84 b*)	3.45 a	<3.12 (2.80 b*)	0.76
Indole <sup>1</sup> ( $\beta$ proton)	3.66 a	3.59 a	3.52 b	3.53 b	3.52 b	3.71 a	3.57 b	0.19
3-Methylindole <sup>1</sup> ( $\alpha$ proton)	3.65 b*	3.39 b*	$\leq$ 3.0 (3.0)	2.94 b*	3.13 b*	3.63 b*	3.25 b*	0.71
2-Methylindole <sup>1</sup> ( $\beta$ proton)	4.06 b*	3.95 b	3.86 b*	3.88 b*	3.88 b*	4.10 b*	3.93 b*	0.24
Ethyl indole-3-carboxylate <sup>2</sup> ( $\alpha$ proton)	Insol.	2.15 c 2.21 c	1.97 c 2.01 c	1.88 d	2.07 c 2.12 c	Insol.	2.22 d	0.25
Ethyl indole-2-carboxylate <sup>3</sup> ( $\beta$ proton)	Insol.	2.77 b*	2.78 b*	2.80 b*	2.80 b*	Insol.	(2.80)	0.03
3-Acetylindole <sup>4</sup> ( $\alpha$ proton)	Insol.	Insol.	1.80 c* 1.83 c	1.66 d	Insol.	Insol.	Insol.	0.17
Indole 3-carboxylic acid <sup>6</sup> ( $\alpha$ proton)	Insol.	Insol.	Insol.	1.82 c 1.86 c	Insol.	Insol.	Insol.	
Indole 2-carboxylic acid <sup>5</sup> ( $\beta$ proton)	Insol.	Insol.	2.77 c 2.80 c	2.80 c 2.82 c	2.72 c* 2.76 c	Insol.	Insol.	0.08
3-Benzoylindole <sup>7</sup> ( $\alpha$ proton)	Insol.	Insol.	Insol.	(2.0)	Insol.	Insol.	Insol.	
2-Benzoylindole <sup>3</sup> ( $\beta$ proton)	Insol.	(2.54 b*)	(2.3)	?	?	?	?	
3-Bromoindole <sup>8</sup> ( $\alpha$ proton)	Insol.	2.96 c 3.00 c	2.56 c 2.59 c	(2.42 c*)	2.76 c 2.78 c	3.10 c 3.15 c	2.93 c 2.96 c	0.54
$\beta$ , $\beta'$ -Diindolylsulphide <sup>9</sup> ( $\alpha$ proton)	Insol.	Insol.	2.80 c 2.83 c	2.62 c 2.66 c	2.86 c 2.90 c	Insol.	—	0.18

NOTE: A question mark indicates that no assignment could be made. The symbol < indicates that the signals for the  $\alpha$  or  $\beta$  protons were certainly less than the values given. Figures in parentheses are tentative assignments. a — triplet; b — multiplet; c — doublet; d — singlet; the asterisk indicates poorly resolved signals. The term "insol." indicates either insoluble or insufficiently soluble to obtain an n.m.r. spectrum.





pounds. The disappearance of the signal upon N-methylation, in the case of indole, supports the assignment of this signal to the  $\text{>N-H}$  proton. Electronegative substituents in the 2 or 3 positions cause a pronounced downfield shift also.

Polar solvents and those which associate with the indole compound (i.e. ethers) cause a larger chemical shift to lower field in the order dimethylsulphoxide  $\rangle$  triethylamine  $\rangle$  acetone  $\rangle$  dioxan.



### SUMMARY

The major points embodied in this research project may be presented as follows:

(a) An investigation of the Williamson ether synthesis involving 3-haloindoles and mercaptans was carried out. While there was some evidence of the formation of the expected thioethers, the method was unsatisfactory due to the decomposition of the haloindoles employed. A reaction in which 3-indolyl mercaptides were treated with benzyl iodide resulted in N-alkylation rather than the anticipated reaction at the sulphur atom.

(b) Attempts made to employ the indole Grignard in reactions with sulphenyl halides to obtain 3-substituted indole derivatives proved unsatisfactory due to the complexity of the reaction. 3-Ethylindole, 3,3'-diindolyl sulphide and at least four other indoles were formed in the reaction along with some of the expected thioether.

(c) The phenylhydrazone of ethylthioacetaldehyde was cyclized under Fischer conditions to yield 3-ethylthioindole. The corresponding oxygen analogue did not produce any isolateable 3-ethoxyindole.

(d) 1,2-Dithiolo[4,3-b]indolo-3(4H)-thione was synthesized followed by its reduction, alkylation and hydrolysis to a 3-alkylthio-2-indolecarboxylic acid. The carboxylic acid could then be converted to the corresponding 3-alkylthioindole by decarboxylation at reduced pressure and elevated temperature.

(e) A method utilizing the effect of solvents on the chemical shift of C<sub>2</sub> and C<sub>3</sub> protons of indoles, was developed as a means to assign C<sub>2</sub> or C<sub>3</sub> substitution in the pyrrole ring of indoles.



## EXPERIMENTAL

All melting points and boiling points recorded in the following pages are uncorrected.

Gas liquid chromatographic analyses were carried out on a Burrell K-2 Kromo-Tog apparatus using either a 2-meter column packed with 20% of Apiezon "L" on Kromat F.B., 30-60 mesh, or one packed with 20% of Silicone Rubber on Kromat F.B., 30-60 mesh. The column temperatures were dependant upon the boiling point of the compounds being used. All compounds were identified by comparison of their retention times with those of authentic samples.<sup>†</sup>

Infrared spectra were recorded on Perkin-Elmer instruments, models 21, 221G and 421.\* Nuclear magnetic resonance spectra were recorded on Varian Associates models A-60 and HR-100 spectrometers.\* Mass spectra were obtained on a MS2-H mass spectrometer,\* Metropolitan Vickers (England). X-ray diffraction spectra were obtained on a Philips Electronics Inc. X-ray Diffraction Unit,\* Type No. 12045.

### 1. Experiments Involving a Williamson-Type Ether Synthesis.

Indole, ethylmercaptoacetate and ethyl mercaptan were obtained as commercial products from Eastman Kodak Co., Inc., New York.

N-Benzoylindole was prepared by the following modification of the method of Weissgerber (63). A mixture of indole (117 g., 1 mole) with 23 g. (1 gram atom) of sodium in 1.5 l. of dioxane was refluxed for 48 hours. To the cooled solution, freed from

<sup>†</sup>Compared on both columns.

\*Department facilities.







unreacted sodium, was slowly added 140.5 g. (1 mole) of benzoyl chloride . The resulting mixture was refluxed an additional 12 hours, then poured into 4 l. of water. The precipitated, crude N-benzoylindole was extracted with pentane to remove unreacted indole. Crystallization of the crude material from ethyl alcohol gave the pure product in 55% yield melting at 67-68°. Lit. m.p., 67-68° (63).

N-Benzoyl-3-bromoindole was obtained by the method of Weissgerber (63). A solution of N-benzoylindole (10 g., 0.045 mole) in 100 ml. of carbon disulphide was maintained at 0° while 7.25 g. (0.045 mole) of cold bromine was added dropwise. When the last of the bromine had been added, the solvent was allowed to evaporate and the residue crystallized from ethyl alcohol giving 11.1 g. (82%) of product melting at 97-98°. Lit. m.p. 97-98° (63).

3-Bromoindole (Method 1) was prepared by the method of Weissgerber (63). N-Benzoyl-3-bromoindole (10 g., 0.033 mole) was added to 100 ml. of 95% ethyl alcohol in which 0.78 g. (0.033 gram atom) of sodium had been dissolved. The resulting solution was warmed on a steam bath for 30 minutes then poured into 1 l. of cold water. The crystalline 3-bromoindole which separated was collected. Yield 5.2 g. (77%) of product melting at 67° (dec.).

3-Bromoindole (Method 2). To a solution of 4.0 g. (0.034 mole) of indole in 40 ml. of reagent pyridine cooled to 0-2°, was added slowly 10.8 g. (0.034 mole) of pyridinium bromide perbromide (Arapahoe Chemicals Inc., Boulder, Colorado, U.S.A.) dissolved in 30 ml. of pyridine. The rate of addition was such that the temperature of the reaction mixture did not rise above 2°. When the



addition was complete, the solution was poured into cold ether and the resulting mixture freed from insoluble material by filtration. The cold ether solution was washed several times with cold dilute 1N hydrochloric acid to remove the pyridine. The residual ether solution of the haloindole was then washed first with cold dilute aqueous sodium hydroxide, then water. The dried ether solution ( $\text{MgSO}_4$ ) was freed from ether and the residue crystallized from n-heptane (decolourized with charcoal if necessary). Yield, 4.3 g. (64%) of pure 3-bromoindole melting at  $65-66^\circ$  (dec.). Lit. m.p.  $67^\circ$  (63).

When dioxane dibromide was used as brominating agent in pyridine solution the same procedure gave 3-bromoindole in 48% yield.

In the recrystallization procedure, it is important not to heat the solution in the presence of any unsolvated 3-bromoindole above  $60^\circ$ , since 3-bromoindole, which deposits in the flask, begins to decompose at  $65^\circ$ . 3-Bromoindole may be kept satisfactorily if placed under a solvent such as pentane and stored at  $-20^\circ$ . Otherwise even very pure material undergoes slow decomposition.

N-Benzoyl-3-chloroindole was prepared by a modification of the method of Weissgerber (63). N-Benzoylindole (30 g., 0.135 mole) in 200 ml. of carbon disulphide, first cooled to  $0^\circ$ , was treated with 16.1 g. (0.135 mole) of sulphuryl chloride. Evaporation of the resulting solution and crystallization of the residue from ethyl alcohol gave 27.6 g. (80%) of crystalline material melting at  $96^\circ$ . Lit. m.p.  $96-97^\circ$  (63).

3-Chloroindole was prepared by the method of Weissgerber (63).





N-Benzoyl-3-chloroindole (5.0 g., 0.02 mole) was treated with 50 ml. of anhydrous ethyl alcohol in which 1.0 g. (0.044 gram atom) of sodium had previously been dissolved. The resulting solution was warmed to 70° for 30 minutes and then poured into 400 ml. of cold water. The crude 3-chloroindole was removed by filtration and crystallized from heptane (charcoal). There was obtained 2.1 g. (71%) of 3-chloroindole melting at 96-97°. Lit. m.p. 98° (63).

Attempted Reaction of 3-Bromoindole with Sodium Ethoxide.

A solution of 0.6 g. (0.026 gram atom) of sodium in 50 ml. of anhydrous ethyl alcohol was heated with 5.0 g. (0.0255 mole) of 3-bromoindole for 2 hours at 60°. The resulting mixture was poured into 250 ml. of cold water. There was recovered 4.7 g. of unreacted 3-bromoindole, melting at 67° (dec.). No 3-ethoxyindole was obtained, indicating that no reaction had occurred between 3-bromoindole and the ethoxide.

Attempted Reaction of 3-Bromoindole with Ethyl Mercaptan.

A solution of 5.0 g. (0.0255 mole) of 3-bromoindole and 3.5 g. (0.026 mole) of anhydrous potassium carbonate in 50 ml. of anhydrous dimethylformamide (138) was treated with 1.6 g. (0.0256 mole) of ethyl mercaptan at 60 for 2 hours. The reaction mixture was then poured into 250 ml. of cold water. Crude 3-bromoindole which precipitated was filtered off and recrystallized from heptane. There was recovered a 93% yield of unreacted 3-bromoindole. No other product was isolated indicative of reaction.

Attempted Reaction of N-sodio-3-bromoindole with Sodium

Ethyl Mercaptide. 3-Bromoindole (5.0 g., 0.0255 mole) in 50 ml.





of anhydrous dioxane was treated with 0.6 g. (0.026 gram atom) of sodium to form N-sodio-3-bromoindole. To the reaction mixture was added a solution of sodium ethyl mercaptide prepared by dissolving 0.6 g. (0.026 gram atom) of sodium in 10 ml. of anhydrous ethyl alcohol followed by the addition of 1.6 g. (0.0258 mole) of ethyl mercaptan to the cooled sodium ethoxide. The resulting dioxane-ethyl alcohol mixture was warmed to 60° for 2 hours then poured into 250 ml. of cold water. 3-Bromoindole was recovered in 86.5% yield, m.p. 67° (dec.).

Reaction of N-Benzoyl-3-bromoindole and Ethyl Mercaptoacetate.

N-Benzoyl-3-bromoindole (10 g., 0.033 mole) in 150 ml. of anhydrous dimethylformamide (138) containing 4.55 g. (0.033 mole) of anhydrous potassium carbonate and 4.0 g. (0.0334 mole) of ethyl mercaptoacetate was warmed to 60 for 2 hours then poured into 500 ml. of cold water. The resulting solution was extracted with ether†(2 x 200 ml.). The combined ethereal extracts were then washed with 0.2 N silver nitrate (2 x 100 ml.) and finally with water (2 x 200 ml.). The ethereal solution was dried over anhydrous magnesium sulphate. Reduction in volume of ether in vacuo resulted in a spontaneous exothermic decomposition yielding HBr and a green amorphous powder. The green material was collected on a Büchner\* and washed with ether. From the combined filtrate and ether washings after removal of the ether there was obtained a yellow oil from which no pure compounds could be recovered by crystallization. Distillation under vacuum resulted in a general decomposition.

Decomposition of 3-Bromoindole in Ether. A solution of 1.0 g.

\* Funnel.

† Peroxide free.



(0.0051 mole) of 3-bromoindole in 10 ml. of ether was evaporated at room temperature overnight. There was formed approximately 800 mg. of a green amorphous material melting at 190-210°. The crude material exhibited a very strong Ehrlich test (71). The infrared spectrum indicated  $\text{>C=N-}$  absorption at 1585  $\text{cm}^{-1}$  (Fig. 1, page 37). The compound gave the following elemental analysis: C, 64.0 %; H, 4.69%; N, 8.65%; and Br, 23.0%. Molecular weight, determined in camphor, gave a value of  $420 \pm 10\%$ . Recrystallization of the material from aqueous ethanol (20% water by weight) gave 450 mg. of a yellow crystalline substance exhibiting a positive Ehrlich test, which decomposed over the range 250-285°. Infra red analysis showed strong  $\text{>N-H}$  absorption at 3460  $\text{cm}^{-1}$  (Fig. 3, page 37).

Methyl Ethyl Ketone Phenylhydrazone was prepared by a modification of the method of E. Fischer (137). Methyl ethyl ketone, 14.4 g. (0.2 mole) in 200 ml. of glacial acetic acid was treated with 21.6 g. (0.2 mole) of phenylhydrazine. The resulting solution was warmed to 50° and stirred for 2 hours at this temperature. The solution was used directly in the following experiment.

2,3-Dimethylindole was prepared by a modification of the method of Marion and Aldfield (95). The phenylhydrazone/acetic acid solution prepared above was treated with 30.2 g. (0.2 mole) of boron trifluoride etherate. An exothermic reaction ensued. After the vigorous reaction had subsided the solution was stirred one half hour then poured into 1 l. of cold water. The resulting mixture was extracted with ether (2 x 200 ml.) and the combined ethereal extracts neutralized with sodium bicarbonate, then dried





over anhydrous magnesium sulphate. Evaporation of the ether and recrystallization of the residue from Skellysolve B afforded a 67% yield of 2,3-dimethylindole, m.p. 105-107°. Lit. m.p. 108° (95).

2,3,3-Trimethylindolenine was prepared by the method of Hoshino (90). Ethylmagnesium iodide was prepared from magnesium (2.4 g., 0.1 mole) and ethyl iodide (16 g., 0.105 mole) in 24 ml. of dry ether. To this solution was added 7.2 g. (0.05 mole) of 2,3-dimethylindole in 20 ml. of ether as quickly as reaction would permit. When the reaction was completed, the excess ethyl iodide and ether were removed by distillation and replaced by 10 ml. of benzene. The mixture was heated to reflux and then methyl iodide (14 g., 0.1 mole) was added to the boiling solution in a dropwise manner. This mixture was refluxed for an additional 2 hours, then cooled and diluted with 2 N acetic acid. The resulting mixture was extracted with ether. The ether extracts were shaken with dilute (2 N) hydrochloric acid to remove basic materials and the layers separated. The aqueous layer was made strongly basic with sodium hydroxide, liberating an oil possessing the odour of safran. This oil was extracted into ether and the solution dried (KOH). Removal of the solvent and distillation of the residual oil at 112-115°/18 mm. gave 5 g. (63%) of liquid 2,3,3-trimethylindolenine. Lit. b.p. 228-229°/744 mm. (90).

Reaction of 3-Bromoindole with Sodium Ethoxide. A solution of 3-bromoindole (5.0 g., 0.025 gram atom) and sodium (0.6 g., 0.0261 mole) dissolved in 50 ml. of dry ethyl alcohol was refluxed under an atmosphere of nitrogen for 24 hours. The solution was





then poured into 250 ml. of cold water and the resulting mixture subsequently extracted with ether (3 x 100 ml.). The combined ethereal extracts were dried ( $\text{MgSO}_4$ ) then freed of solvent. The residue was crystallized from pentane yielding 2.8 g. (93%) of indole, m.p.  $52^\circ$ . A mixed melting point with authentic indole showed no depression. The infrared spectrum was identical to that of indole. The aqueous phase was acidified with dilute  $\text{HNO}_3$  and treated with 50 ml. of 1 N silver nitrate solution. The silver bromide weighed 4.67 g. indicating 100% decomposition of the 3-bromoindole.

Reaction of 3-Chloroindole with Sodium Ethoxide. This reaction was carried out as above except that 3.86 g. (0.0255 mole) of 3-chloroindole was substituted for 3-bromoindole. In this case 1.2 g. of indole was recovered. Acidification of the aqueous phase with  $\text{HNO}_3$  and addition of silver nitrate, resulted in precipitation of  $\text{AgCl}$  indicating the presence of chloride ion.

Reaction of 3-Bromoindole with 95% Ethyl Alcohol. This reaction was carried out as above except that sodium was omitted and 95% ethyl alcohol substituted for anhydrous ethyl alcohol and the solution refluxed for 12 hours. There was recovered 2.5 g. (84%) of indole.

Reaction of 3-Bromoindole with Aqueous Ethyl Alcohol. This reaction was carried out as above, except that aqueous ethyl alcohol (20%  $\text{H}_2\text{O}$  by weight) was substituted for 95% ethyl alcohol. Nineteen grams (64%) of indole was recovered.

Decomposition of 3-Bromoindole in Dimethylformamide Containing Potassium Carbonate. 3-Bromoindole (5.0 g., 0.0255 mole) with



3.52 g. (0.0255 mole) of anhydrous potassium carbonate in 100 ml. of anhydrous dimethylformamide was heated at  $150^{\circ}$  for 12 hours during which  $\text{CO}_2$  was evolved (absorbed in saturated  $\text{Ca}(\text{OH})_2$  solution). The mixture was then poured into 500 ml. of cold water. This solution was extracted with ether (3 x 200 ml.). The ethereal extract was dried ( $\text{MgSO}_4$ ) and freed from ether. Crystallization of the residue from pentane resulted in 2.6 g. (87.4%) of indole, m.p.  $52^{\circ}$  (identical with authentic indole in m.p. and I.R.). Bromide ion determined as above resulted in 4.65 g. of  $\text{AgBr}$ , accounting for 97.5% of the theoretical amount of bromine in 3-bromoindole.

Decomposition of 3-Chloroindole in Dimethylformamide Containing Potassium Carbonate. The experiment was carried out as the one above except that 3.86 g. (0.0255 mole) of 3-chloroindole was substituted for 3-bromoindole. In this case 2.3 g. (77%) of indole was obtained.

Decomposition of 3-Bromoindole in Dimethylformamide at  $60^{\circ}$ . This reaction was carried out as described for the  $150^{\circ}$  reaction. Silver bromide, 0.835 g., was recovered, accounting for 17.5% of available bromine.

Attempted Decomposition of 3-Bromoindole with Dimethylformamide in the Absence of Potassium Carbonate. 3-Bromoindole (5.0 g., 0.0255 mole) was heated to  $150^{\circ}$  in 100 ml. of anhydrous dimethylformamide under an atmosphere of nitrogen for 12 hours. Dilution of the resulting solution with 500 ml. of cold water resulted in precipitation of 4.8 g. (96%) of unreacted 3-bromoindole, m.p.  $67^{\circ}$  (dec.).





Decomposition of 3-Bromoindole with Dimethylformamide Containing Water. This reaction was carried out as described above except that 10 ml. of water was added to 100 ml. of the dimethylformamide. There was recovered 1.6 g. (32%) of 3-bromoindole and 2.72 g. of silver bromide accounting for 57% of the available bromine.

Attempted Decomposition of 3-Bromoindole with Potassium Carbonate in Dioxane. 3-Bromoindole (5.0 g., 0.0255 mole) with 3.86 g. (0.0255 mole) of anhydrous potassium carbonate in 100 ml. of anhydrous dioxane was refluxed for 12 hours. Dilution of this solution with 500 ml. of cold water resulted in precipitation of 4.8 g. (96%) of unreacted 3-bromoindole, m.p.  $67^{\circ}$  (dec.). No indole was detected by G.L.C. of the dioxane solution.

Attempted Decomposition of 3-Bromoindole with Potassium Carbonate in Cyclohexene. 3-Bromoindole (5.0 g., 0.0255 mole) with 3.86 g. (0.0255 mole) of anhydrous potassium carbonate in 150 ml. of cyclohexene was refluxed 12 hours. The resulting solution was filtered and poured into 200 ml. of pentane. A precipitate of 4.5 g. (90%) of unreacted 3-bromoindole was recovered. No indole was detected by G.L.C. of the cyclohexene solution.

Reaction of 3-Bromoindole with Phenyllithium. Lithium metal (0.35 g., 0.05 gram atom), cut into small pieces, was added to 50 ml. of anhydrous ether under an atmosphere of nitrogen. To this was added dropwise a solution composed of 4.0 g. (0.0255 mole) of bromobenzene in 10 ml. of dry ether. Upon completion of the addition the solution was then filtered under  $N_2$  and added drop-





wise to a solution of 4.90 g. (0.025 mole) of 3-bromoindole in 200 ml. of cyclohexene. The resulting solution darkened immediately upon the addition of phenyllithium. Upon completion of the addition the mixture was refluxed 30 minutes, then filtered hot and finally cooled. Removal of the solvents yielded a tar which by T.L.C. (thin layer chromatography) using benzene as eluant, indicated at least 17 compounds exhibiting a positive Ehrlich test. No pure substance was isolable.

Reaction at 60° of N-Benzoyl-3-bromoindole and Ethyl Mercaptan in Dimethylformamide Containing Potassium Carbonate. This reaction was carried out in the same manner as that reaction described earlier between N-benzoyl-3-bromoindole, ethyl mercaptoacetate and potassium carbonate (page 118). The only change was the substitution of 2.1 g. (0.034 mole) of ethyl mercaptan for the ethylmercaptoacetate. Workup of the products resulted in a similar decomposition yielding the same greenish amorphous material (I.R.) as isolated in the previous case.

Reaction of N-Benzoyl-3-bromoindole with Ethyl Mercaptan in Dioxane. A mixture of N-benzoyl-3-bromoindole (10 g., 0.033 mole) with 4.55 g. (0.033 mole) of anhydrous potassium carbonate in 200 ml. of anhydrous dioxane and 2.1 g. (0.034 mole) of ethyl mercaptan was refluxed for 12 hours. The cooled reaction mixture was poured into 1 l. of cold water and the solution then extracted with ether (3 x 200 ml.). The combined ether extracts were washed with 0.2 N silver nitrate (2 x 100 ml.) and H<sub>2</sub>O (2 x 200 ml.) and then dried (MgSO<sub>4</sub>). The ether was concentrated in volume to about 40 ml. and poured into 200 ml. of Skellysolve "B" whereupon 3-bromoindole



precipitated, 4.5 g. (69.5%); m.p., 67° (dec.). The filtrate from the 3-bromoindole was freed from solvent and the resulting oil distilled. The distillation was accompanied by considerable decomposition. However ethyl thiolo benzoate, 2.1 g. (35.7% based on N-benzoyl-3-bromoindole) distilled over at 122°/15 mm. (lit. b.p., 118-122°/15 mm.) (107). The infrared spectrum was identical with that of authentic ethyl thiolo benzoate.

Reaction at 150° of N-Benzoyl-3-bromoindole with Ethyl Mercap-  
tan and Potassium Carbonate in Dimethylformamide. This reaction was carried out as described earlier, except that reaction temperature was maintained at 150° for 12 hours. Isolation of the reaction products was carried out as before (page 124). An aliquot of the ethereal extract was subjected to G.L.C. and showed peaks with retention times equivalent to those of diethyl disulphide, indole, ethyl thiolo benzoate and 3-ethylindole. At least four other compounds were indicated. A 10 ml. aliquot of the ethereal extract, when treated with 2 ml. of alcoholic HgCl<sub>2</sub> (sat.), gave a precipitate identified as ethylthiomercuric chloride, comparative I.R. and X-ray scatter patterns (Fig. 7, page 53). A vacuum distillation of the remainder of the ethereal extract gave 1.6 g. of indole (28.4% based on N-benzoyl-3-bromoindole), b.p. 104°/5 mm.; 2.63 g. of ethyl thiolo benzoate (48% based on N-benzoyl-3-bromoindole), b.p. 108-110°/5 mm.; and 1.23 g. of 3-ethylindole (24.5% based on N-benzoyl-3-bromoindole), b.p., 138-140°/1.5 mm.. The indole and 3-ethylindole were identified by melting point and mixed melting point and comparative infrared spectra of the respective picrates with those of authentic samples. Ethyl thiolo-





benzoate (107) was identified by comparative infrared spectra.

Ethyl Thioloobenzoate was prepared by a modification of the method of Hantzsch and Scharf (107). A solution of 6.2 g. (0.1 mole) of ethyl mercaptan in 50 ml. of anhydrous dimethylformamide containing 13.8 g. (0.1 mole) of anhydrous potassium carbonate was treated with 14.0 g. (0.1 mole) of benzoyl chloride. The resulting mixture was refluxed for 2 hours then poured into 200 ml. of water. The aqueous mixture was extracted with ether (3 x 100 ml.) and the combined extracts were dried over magnesium sulphate. The ether was removed under reduced pressure, and the remaining oil distilled. B.p.  $146^{\circ}/31$  mm.. Lit. b.p.  $146^{\circ}/31$  mm. (107).

Ethylthiomericuric chloride was prepared by the method of Challenger and Rawlings (98). Mercuric chloride (3 g.) in water (80 ml.) was added to ethyl mercaptan (2 g., 0.048 mole). A red precipitate was immediately formed, which quickly become pink and finally white. Next day the solid was separated and found to melt at  $73^{\circ}$ . One crystallization from alcohol raised the melting point of diethylthio mercury to  $76-77^{\circ}$ , which further crystallization failed to improve. Mercuric chloride (1.6 g.) in water (30 ml.) was then added to the original filtrate, giving a white solid, m.p.  $86^{\circ}$ . Extraction of this with alcohol left a residue of ethylthiomericuric chloride,  $C_2H_5 \cdot HgCl$ , unmelted at  $260^{\circ}$ .

2-Ethylindole was prepared by the method of Verley and Beduwé (103). A mixture of one part of o-propionotoluidide with 2.5 parts of sodium amide was cautiously heated in a metal vessel to  $200^{\circ}$ . Ammonia was evolved as the solid began to melt and the





sodium derivative of o-propionotoluidide was formed. The temperature of the pasty mass was raised slowly to  $250^{\circ}$  where it remained till the ammonia evolution was almost completed. Water was cautiously added to the cooled material and the mixture then steam distilled. The 2-ethylindole was readily separated from the aqueous distillate, taken up in ether and dried ( $\text{MgSO}_4$ ), then distilled at  $142-143^{\circ}/5$  mm.. Lit. b.p.  $143^{\circ}/5$  mm..

3-Ethylindole was prepared by a modification of the method of Korczynski et al. (105). *n*-Butyraldehyde (14.4 g., 0.2 mole) was treated with 21.6 g. (0.2 mole) of phenylhydrazine in 200 ml. of glacial acetic acid. The resulting solution was warmed to  $50^{\circ}$  and stirred for 2 hours. The solution was allowed to cool to room temperature and 30.2 (0.2 mole) of boron trifluoride etherate added. An exothermic reaction ensued. When the reaction had subsided, the mixture was stirred for an additional  $\frac{1}{2}$  hour, then poured into 1 l. of  $\text{H}_2\text{O}$  and the resulting material extracted with ether (3 x 200 ml.). The ethereal extracts were neutralized with  $\text{NaHCO}_3$ , washed with water (2 x 200 ml.) and dried ( $\text{MgSO}_4$ ). The ether was removed on a rotary evaporator and the resulting oil distilled at  $175^{\circ}/6$  mm.. Lit. b.p.  $282-284^{\circ}/730$  mm. (105). Addition of a saturated solution of picric acid in ethanol to 3-ethylindole resulted in formation of a picrate melting at  $143^{\circ}$ . Lit. m.p.  $143^{\circ}$  (105).

Attempted Reaction Between Indole and Ethyl Mercaptan in Dimethylformamide. A mixture of indole (6.9 g., 0.059 mole), 3.64 g. (0.059 mole) of ethyl mercaptan and 8.1 g. (0.059 mole) of anhydrous potassium carbonate in 100 ml. of anhydrous dimethyl-



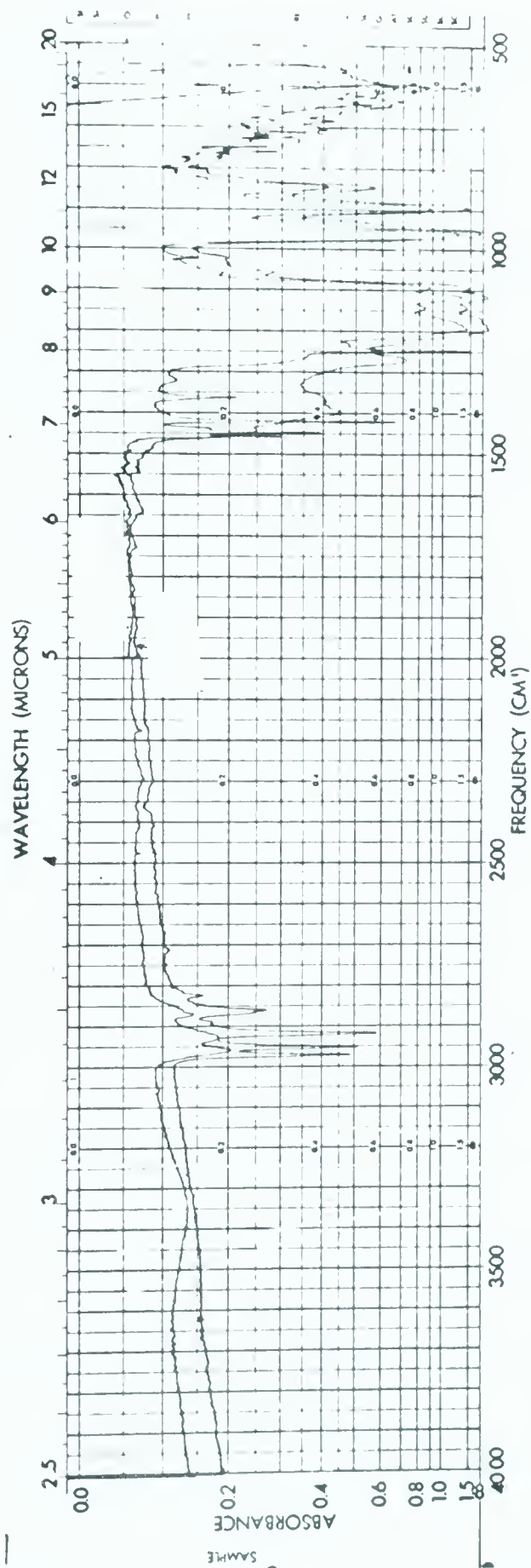


Fig. 35. Comparative I.R. Spectrum of Silver Ethyl Mercaptide.  
(Halo Oil mull.)



formamide was refluxed for 6 hours at 150°. The cooled reaction products were poured into 1 l. of cold water. The aqueous mixture was extracted with ether (2 x 200 ml.) and the combined ethereal extracts were washed with 0.2 N aqueous silver nitrate solution (3 x 100 ml.) then dried (MgSO<sub>4</sub>). G.L.C. and T.L.C. of this solution indicated only unreacted indole.

Attempted Reaction Between 3-Bromoindole and Ethyl Thiolo-benzoate. A mixture of 3-bromoindole (5 g., 0.0255 mole) and 5 g. (0.03 mole) of ethyl thiolo-benzoate was distilled at 146°/31 mm.. Much decomposition, attributed to 3-bromoindole, was observed. The distillate contained only ethyl thiolo-benzoate (I.R.).

Attempted Reaction Between Ethyl thiolo-benzoate or Ethyl Disulphide and Mercuric Chloride. A sample (1 g.) of each of diethyl disulphide and ethyl thiolo-benzoate was added to separate 10 ml. quantities of saturated alcoholic mercuric chloride. On standing 48 hours the solution deposited no ethylthiomeric chloride.

N-(o-Carboxyphenyl)Glycine was prepared by the method of A. Etienne (101). A solution of anthranilic acid (150 g., 1.1 moles) and 99 g. (1.1 moles) of chloroacetic acid in 1 l. of water was treated with 130 g. (1.1 moles) of sodium carbonate monohydrate. The resulting solution was heated to 100° for two hours. The mixture was acidified with conc. HCl. The precipitated N-(o-carboxyphenyl)glycine was collected on a Büchner funnel and crystallized from methyl alcohol. Yield, 35 g. (16%), m.p. 218°.

N-(o-Carboxyphenyl)-glycine diethyl ester was prepared by the method of A. Etienne (101). N-(o-Carboxyphenyl)glycine (20 g.,





0.1025 mole) in 200 ml. of anhydrous ethyl alcohol containing 30 ml. of concentrated sulphuric acid was refluxed for 14 hours. The resulting solution was then poured into 1 l. of cold water and allowed to stand for 24 hours. The crude diester was collected and crystallized from ethyl alcohol (aqueous) giving a 15 g. (58.2%) yield of the phenylglycine diethyl ester melting at  $76^{\circ}$ .

2-Carbethoxyindoxyl was prepared by the method of A. Etienne (101). Sodium (2.0 g., 0.087 mole) was dissolved in 15 ml. of anhydrous ethyl alcohol. The solution was cooled to  $25^{\circ}$  and then treated with 25 ml. of anhydrous ether and 10 g. (0.04 mole) of N-(o-carbethoxyphenyl)glycine ethyl ester and the resulting mixture refluxed for 1.5-2 hours. The cooled mixture was poured into 200 ml. of cold water and acidified with acetic acid. The resulting precipitate was washed with water and crystallized from aqueous ethanol. There was obtained a 7.4 g. (90%) yield of 2-carbethoxyindoxyl, melting at  $116^{\circ}$ .

2-Carbethoxy-3-ethoxyindole was prepared by a modification of the method of A. Etienne (101). To a solution of 8 g. (0.039 mole) of 2-carbethoxyindoxyl in 30 ml. of ethyl alcohol containing 30 ml. of water was added 5.5 g. (0.0398 mole) of ethyl sulphate. The resulting mixture was heated on a steam bath for 30 minutes, then poured into 200 ml. of water. The solid organic material was separated by filtration and crystallized from pentane, resulting in colourless crystals, 8 g. (88%) melting at  $97-98^{\circ}$ . Lit.  $98^{\circ}$  (102).

3-Ethoxyindole-2-carboxylic acid was prepared by a modifi-



cation of the method of Baeyer (102). 2-Carbethoxy-3-ethoxy-indole (11.65 g., 0.05 mole) in 100 ml. of 95% ethyl alcohol was refluxed for 2 hours with 5.6 g. (0.1 mole) of potassium hydroxide in 100 ml. of water. Acidification of the cooled mixture gave 7.25 g. (71%) of crude 3-ethoxyindole-2-carboxylic acid, which upon crystallization from aqueous ethanol melted at 159-160°. Lit. m.p. 160° (102).

3-Ethoxyindole was obtained by a modification of the method of A. Etienne (101). A quantity of 3-ethoxyindole-2-carboxylic acid (2.0 g., 0.01 mole) was heated in a distilling flask at 6 mm.. A gentle evolution of gas (CO<sub>2</sub>) occurred and the residual material distilled at 160°/6 mm. giving 1.4 g. (87.5%) of 3-ethoxyindole. The indole is unstable and must be refrigerated under nitrogen.

3,3'-Diindolyl disulphide was prepared by the method of Woodbridge and Dougherty (80). A mixture of indole (23.4 g., 0.2 mole) and thiourea (46.5 g., 0.61 mole) was treated with 50.8 g. (0.2 mole) of iodine dissolved in 400 ml. of ethyl alcohol and 200 ml. of water. After the addition was complete the solution was made basic with sodium hydroxide. The resulting solution was diluted with 500 ml. of water and stirred overnight. There was obtained 6.9 g. (23%) of 3,3'-diindolyl disulphide melting at 227-229.5° upon crystallization from toluene. Lit. m.p. 217-218° (76).

N-Benzylindole was prepared by the method of Plieninger (110). Finely powdered sodium amide (3.9 g., 0.1 mole) was dissolved in 200 ml. of liquid ammonia containing 11.3 g. (0.1 mole) of indole. To this was added in a dropwise manner a solution of 12 g. (0.1 mole) of benzyl chloride in 10 ml.





of absolute ether. After the resulting mixture had been stirred for one hour, the ammonia was allowed to evaporate and the residue was treated with 20 ml. of methanol-ether (1:1), then poured into 100 ml. of water. The ethereal layer was dried ( $\text{Na}_2\text{SO}_4$ ). The ether was removed by evaporation and the residue was distilled at  $172-175^\circ/1-2$  mm. yielding 9.4 g. (60%) of crude N-benzylindole melting at  $44^\circ$ . Crystallization from ethanol raised the melting point to  $56^\circ$ .

N,N'-Dibenzyl-3,3'-Diindolyl Disulphide. To a solution of 0.72 g. (0.019 mole) of lithium aluminum hydride in anhydrous tetrahydrofuran under an atmosphere of nitrogen was added 10 g. (0.0338 mole) of 3,3'-diindolyl disulphide in 60 ml. of anhydrous tetrahydrofuran all at  $25^\circ$ . The resulting solution was stirred for 30 minutes, and this was followed by the successive addition of 20 ml. of 5 N aqueous sodium hydroxide and 14.6 g. (0.067 mole) of benzyl iodide in 60 ml. of anhydrous tetrahydrofuran. The mixture was refluxed for 48 hours, then diluted with 500 ml. of cold water. The resulting precipitate, when chromatographed on neutral alumina (activity grade 1) using methylene chloride as eluant (combining all fractions), gave 6.0 g. (37.1%) of yellow material. Crystallization of this product from ethanol yielded a yellow crystalline material melting at  $150-151.5^\circ$ . The compound exhibited a weak Ehrlich test and showed no  $>\text{N}-\text{H}$  absorption in the infrared region  $3300-3600\text{ cm}^{-1}$  (Fig. 8, page 53). A nuclear magnetic resonance spectrum indicated aliphatic protons at  $4.96\tau$  (singlet) and signals in the region  $2.49-3.30\tau$  attributed to aromatic protons. An analytical sample was prepared by crystal-



lization from ethyl propionate, yielding yellow crystals melting over the range 151-153°.

Calc. for  $C_{30}H_{24}N_2S_2$ : C, 75.5; H, 5.04; N, 5.88; S, 13.45.

Found: C, 75.14; H, 5.27; N, 5.67; S, 13.29.

A small quantity (282 mg.) of this compound was mixed with 5 g. of active Raney nickel (139) in 50 ml. of anhydrous ethyl alcohol and the solution refluxed for 24 hours. The hot solution was filtered free of Raney nickel, and the nickel was washed with several 50 ml. portions of hot ethyl alcohol. The alcohol extracts were combined and freed from solvent by distillation affording 45 mg. of a compound melting at 35-39°. This compound when treated with 10 ml. of a saturated ethanolic solution of picric acid yielded a picrate melting at 76-78°. This picrate on admixture with the picrate of N-benzylindole(110) melted at 76-78°. The infrared spectrum of this picrate was identical with that of an authentic sample (110).

## 2. Experiments Involving the Indole Grignard.

Ethyl Disulphide was obtained as a commercial product from Eastman Kodak Co. Inc., New York, New York, U.S.A..

Sulphuryl Chloride was obtained as a commercial product from Eastman Kodak Inc., New York, New York, U.S.A..

Ethyl Sulfenyl Chloride was prepared by a modification of the method of Brentzinger et al. (111). Ethyl disulphide, 60 g. (0.408 mole) in a 1-litre flask, protected with a  $CaCl_2$  drying tube, was cooled to -70° in a dry ice-acetone mixture. To this was added dropwise 55 g. (0.408 mole) of sulphuryl chloride. The





solution became orange immediately upon addition of the first portions of sulphuryl chloride. During the addition the solution was slowly allowed to warm to room temperature, thus preventing precipitation of the reactants. Upon completion of the addition, the reaction mixture was heated on a steam bath for 20 minutes to aid in removal of dissolved  $\text{SO}_2$ . The compound was then distilled at  $51^\circ/74$  mm.. Yield, 70%. Lit. b.p.  $51^\circ/74$  mm. (111).

Reaction of Indolylmagnesium Bromide with Ethyl Sulfenyl Chloride. Ethyl bromide (26.1 g., 0.24 mole) in 600 ml. of anhydrous ether was treated with 6 g. (0.25 mole) of magnesium turnings. When the reaction was complete 27 g. (0.23 mole) of indole in 50 ml. of dry ether was added. To the resulting indolylmagnesium bromide was added dropwise 23.1 g. (0.24 mole) of ethyl sulfenyl chloride in 50 ml. of anhydrous ether so that the reaction mixture was maintained at  $-10^\circ$ . The mixture slowly became deep red. Upon completion of the addition the vessel and contents were allowed to come to room temperature, whereupon the solution was refluxed for 3 hours. The contents of the flask was cooled and poured into 2 l. of water and the pH adjusted to 7 by the addition of acetic acid. The ether layer was separated and the aqueous layer extracted with ether (2 x 200 ml.). The ethereal solutions were combined and reduced in volume to about 400 ml.. This solution was extracted with water (3 x 200 ml.) and treated with 0.2 N aqueous silver nitrate (2 x 100 ml.) yielding 1.5 g. of silver ethyl mercaptide whose infrared spectrum was identical with that of a sample prepared from silver nitrate and ethyl mercaptan (Fig. 35, page 128). The remaining ether filtrate was





then completely freed of solvent and gave a brown oil which, when taken up in ethyl alcohol and cooled to  $-20^{\circ}$  overnight, precipitated 5.1 g. of 3,3'-diindolyl sulphide. After one crystallization from toluene the sulphide melted at  $232^{\circ}$ . Lit. m.p.  $232^{\circ}$  (73).

Calc. for  $C_{16}H_{12}N_2S$ : C, 72.73; H, 4.65; N, 9.44; S, 12.12.

Found: C, 72.76; H, 4.61; N, 9.47; S, 11.94.

The filtrate obtained from the precipitated 3,3'-diindolyl sulphide was evaporated and the resulting oil divided into two equal portions. One portion was subjected to vacuum distillation resulting in 2.1 g. of indole, b.p.  $110^{\circ}/6$  mm. and 3.8 g. of 3-ethylindole, b.p.  $170^{\circ}/3$  mm.. The indoles were identified by melting points of their respective picrates, mixed melting points of picrates and comparative infrared spectra of those of authentic samples. Portions of the remaining half of the filtrate were subjected to G.L.C. analysis. This showed peaks with retention times which were identical with those for authentic indole, 3-ethylindole and 3-ethylthioindole. Another aliquot treated with saturated alcoholic mercuric chloride solution precipitated ethylthiomercuric chloride which was identified by comparison of its infrared spectrum with that of an authentic sample (105). At least four other unidentified compounds are indicated by the presence of peaks in the gas liquid chromatogram. Thin layer chromatography yielded similar results but showed in addition evidence for the presence of 3,3'-diindolyl, identified by its retention time and characteristic fluorescence and Ehrlich test compared with those of an authentic sample (112).

3,3'-Diindolyl-2,2'-tetrasulphide was prepared by the method



of Carpenter, Grant and Snyder (112). A mixture of 11.7 g. (0.1 mole) of indole, 9.6 g. (0.3 mole) of sulphur and 50 ml. of dimethylformamide was stirred under nitrogen and heated by an oil-bath at  $145^{\circ}$  for 3 hours, and then allowed to cool slowly overnight in the oil bath. The yellow crystals which appeared were removed and thoroughly washed with carbon disulphide. Removal of the solvent gave 10.5 g. (59%) of reasonably pure 3,3'-diindolyl-2,2'-tetrasulphide, m.p.  $300-305^{\circ}$ .

3,3'-Diindolyl was prepared by the method of Carpenter, Grant and Snyder (112). One hundred grams of water-wet Raney nickel (139) was activated by washing with 300 ml. of 95% ethanol. The nickel, along with 3.18 g. (0.0089 mole) of 3,3'-diindolyl-2,2'-tetrasulphide in 200 ml. of 95% ethanol, was heated under reflux for 5.5 hours. The mixture was filtered while hot. The filter cake was washed with dimethylformamide (3 x 50 ml.). The filtrate and washings were combined and diluted with enough water to completely precipitate the organic material, which was subsequently removed by filtration and then desiccated over phosphorus pentoxide. The yield of crude 3,3'-diindolyl, a white solid, melting at  $250-285^{\circ}$ , was 0.826 g. (40%). This material was recrystallized once from ethyl acetate and once from toluene and then dried for 20 hours at  $25^{\circ}$  (0.2 mm.), m.p.  $284-286^{\circ}$ . Lit. m.p.  $286-287^{\circ}$  (113).

3,3'-Diindolyl Sulphide was prepared by the method of Madelung and Tencer (73). A quantity of magnesium turnings 2.5 g., (0.104 mole) in 100 ml. of anhydrous ether was treated with 11 g.







(0.101 mole) of ethyl bromide in 25 ml. of dry ether. Upon completion of the reaction, 12 g. (0.1025 mole) of indole in 50 ml. of anhydrous ether was added dropwise. When evolution of ethane had ceased 3.2 g. (0.10 mole) of finely powdered sulphur was added in one portion. The solution was rapidly stirred for 1 hour, the ether then separated by filtration and the filter cake broken up under dilute 1 N HCl then filtered. Extraction of the resulting precipitate with hot ethyl alcohol, then cooling the ethanolic extract deposited 5.0 g. (20%) of 3,3'-diindolyl sulphide. Crystallization from toluene afforded colourless needles melting at  $232^{\circ}$ .

Attempted Reaction of Indole Magnesium Bromide with 3-Ethylthioindole. Magnesium turnings, 1.2 g. (0.05 mole) in 50 ml. of anhydrous ether were treated with 5.5 g. (0.05 mole) of ethyl bromide in 10 ml. of dry ether. On completion of the reaction 6 g. (0.05 mole) of indole in 25 ml. of dry ether was quickly added. When the evolution of ethane had ceased (about  $\frac{1}{2}$  hr.) the mixture was cooled to  $0^{\circ}$  and 8.85 g. (0.05 mole) of 3-ethylthioindole in 10 ml. anhydrous ether added dropwise. The resulting solution was warmed to reflux temperature and maintained there for 3 hours. It was then worked up in the same manner as for the reaction of indolylmagnesium bromide with ethyl sulfenyl chloride, page 134. G.L.C. indicated only two peaks with retention times equivalent to indole and 3-ethylthioindole. The products taken up in cold ethyl alcohol could not be induced to crystallize.

Attempted Reaction of Indole Dimagnesium Bromide with 3-Ethylthioindole. The reaction was carried out as in the experiment



described immediately preceding, except that 2.4 g. (0.10 mole) of magnesium turnings, and 11 g. (0.10 mole) of ethyl bromide was substituted. The same result was obtained as above.

Air-Oxidation of the Indole Mono-Grignard. The indole mono-Grignard was prepared as described in the preceding experiment and stirred at room temperature for 24 hours, with no precaution taken for the exclusion of dry air. A work-up of the products in the usual manner yielded impure indole. Thin layer chromatography indicated the formation of 3,3'-diindolyl by its characteristic Ehrlich reaction and retention times compared with those of an authentic sample (112). At least 9 different indoles are indicated.

The Reaction of Phenylmagnesium Bromide with Ethyl Sulfenyl Chloride. Magnesium turnings, 1.2 g. (0.05 mole) in 50 ml. of anhydrous ether, were treated with 8 g. (0.05 mole) of bromobenzene in 10 ml. of dry ether. When the reaction was completed, the products were cooled to 0° and 4.8 g. (0.05 mole) of ethyl sulfenyl chloride in 10 ml. of dry ether added dropwise to the cooled solution. The solution was then warmed to reflux for 2 hours, cooled and worked up in the manner described for the reaction of indole magnesium bromide with ethyl sulfenyl chloride, page 134. Gas liquid chromatography indicated only benzene and ethyl phenyl sulphide. There was no evidence of ethylbenzene or chlorobenzene.

The Reaction of Phenylmagnesium Bromide with Ethyl Sulfenyl Chloride. The reaction was carried out as above except that 2.4 g. (0.10 mole) of magnesium turnings were substituted, and 12.8 g.





(0.05 mole) of p-dibromobenzene substituted for brombenzene.

G.L.C. yielded the same results as in the above experiment.

Attempted Reaction of Indole Magnesium Bromide with 3,3'-Diindolyl Disulphide. Magnesium turnings 1 g. (0.0416 mole) in 50 ml. of dry ether were treated with 6.16 g. (0.0395 mole) of ethyl iodide in 10 ml. of anhydrous ether. On completion of the reaction 4.68 g. (0.04 mole) of indole in 10 ml. of dry ether was added dropwise. After the addition of the indole 4.0 g. (0.00135 mole) of 3,3'-diindolyl disulphide in 10 ml. of anhydrous tetrahydrofuran was added dropwise. The resulting mixture was refluxed for 2 hours, then poured into 400 ml. of ice water and the mixture filtered. The filtrate, dried ( $\text{MgSO}_4$ ) and extracted in a Soxhlet extractor with pentane, gave a recovery of 3.5 g. of indole. Extraction with toluene resulted in recovery of 3.75 g. of unreacted 3,3'-diindolyl disulphide. No 3,3'-diindolyl sulphide was detected.

### 3. Experiments Involving Miscellaneous Attempts to Produce 3-Alkylthioindoles.

Bromoacetaldehyde Diethyl Acetal was obtained as a commercial product from Matheson, Coleman and Bell. East Rutherford, New Jersey, U.S.A..

Ethylthioacetaldehyde Diethyl Acetal was prepared by the method of Eirkofer and Storch (124). Forty grams (1.74 gram atoms) of sodium was dissolved in 660 ml. of absolute alcohol and the solution cooled to  $0^\circ$ . Bromoacetaldehyde diethyl acetal, 316 g. (1.615 mole) was added dropwise over a period of three hours.





After standing overnight the solution was treated with 500 ml. of water, and the mixture extracted with ether (3 x 200 ml.). The ethereal extracts were combined and dried ( $K_2CO_3$ ). The ether was removed in vacuo and the remainder distilled at reduced pressure affording 155.6 g. (54.2%) of ethylthioacetaldehyde diethyl acetal boiling at 75-85 /14 mm.. Lit. b.p. 75-85 /14 mm. (124).

Boron Trifluoride Etherate was obtained as a commercial product from Eastman Kodak Co. Inc. New York, New York, U.S.A..

3-Ethylthioindole (1). A mixture of 17.8 g. (0.1 mole) of ethylthioacetaldehyde diethyl acetal and 10.8 g. (0.1 mole) of phenylhydrazine was added to 100 ml. of glacial acetic acid. A slightly exothermic reaction ensued. Addition of 15.1 g. (0.1 mole) of boron trifluoride etherate caused slow exothermic reaction in which a rise of  $65^{\circ}$  ( $25 \rightarrow 90^{\circ}$ ) in the reaction mixture was experienced. The products were maintained at  $90^{\circ}$  for 1 hour then poured into 1 l. of water. The aqueous mixture was extracted with ether (3 x 200 ml.). The combined ether extracts were neutralized with sodium bicarbonate and washed successively with water (1 x 300 ml.), 1 N HCl (3 x 300 ml.) and finally with water (3 x 300 ml.). The ethereal solution was dried ( $MgSO_4$ ) and the ether removed in vacuo. There was obtained 11.95 g. (67.5%) of red oil which was reasonably pure 3-ethylthioindole as shown by G.L.C.. An analytical sample was prepared by chromatographing a portion on neutral alumina (activity grade 1) using benzene as eluant. The benzene eluant was freed of solvent and the residual oil distilled at  $95^{\circ}/1.5$  mm.. Distillation was accompanied by considerable decomposition. The chromatographic procedure and



distillation was carried out a second time on the same material affording 1.59 g. (9% yield) of a light yellow oil boiling at  $95^{\circ}/1.5$  mm.,  $n_D^{24}$ , 1.6285. An infrared spectrum of this compound (neat) indicated  $>NH$  by absorption at  $3410\text{ cm}^{-1}$  and aliphatic protons absorbing at 2885, 2915 and  $2980\text{ cm}^{-1}$  (Fig. 18, page 84). A nuclear magnetic resonance spectrum obtained from a solution of this compound in deuteriochloroform (Fig. 19, page 83) revealed a triplet at  $8.80\tau$ ,<sup>\*</sup> a quartet at  $7.31\tau$ <sup>\*</sup> both characteristic of an ethyl group. Signals at  $2.0-3.0\tau$ , were attributed to aromatic protons. Mass spectrometric observations are discussed in the appendix. The compound resisted acetylation by acetic anhydride/benzene and acetyl chloride/pyridine. Treatment of 3-ethylthioindole with picric acid failed to give a well defined picrate. The substance obtained melted at  $-10^{\circ} - 0^{\circ}$ .

Fifty-five mg. ( $2.55 \times 10^{-4}$  mole) of analytically pure 3-ethylthioindole was treated with 69 mg. ( $2.55 \times 10^{-4}$  mole) of mercuric chloride in 1.0 ml. of 95% ethyl alcohol. On standing overnight the solution deposited 50 mg. of ethylthiomercuric chloride. (Identified by comparison of its infrared spectrum with that of an authentic sample.) A thin layer chromatogram of the remaining ethanolic solution showed spots developed by the use of Ehrlich's reagent. The  $R_f$  values of these spots were identical to those of authentic samples of indole and 3-ethoxyindole (102).

Ethoxyacetaldehyde Diethyl Acetal was prepared by the method of Leuchs and Geiger (127). Forty-five grams (1.5 gram atom) of sodium was dissolved in 800 ml. of absolute alcohol and the result-

<sup>\*</sup> $J=7$  c.p.s.    <sup>\*\*</sup> Calc. for  $C_{10}H_{11}NS$ : C, 67.73; H, 6.26; N, 7.95; S, 18.07.  
Found; C, 67.54; H, 6.19; N, 7.74; S, 18.27.







ing solution then treated with 200 g. (1.31 mole) of chloroacetaldehyde diethyl acetal and finally heated in an autoclave for one hour each at 120°, 140° and 160° respectively. The cooled reaction mixture was neutralized (methyl orange) with alcoholic hydrochloric acid and the sodium chloride removed by filtration. The solution was then distilled under vacuum. The chief portion distilled at 72-74°/26 mm. yielding 141 g. (66%) of ethoxyacetaldehyde diethyl acetal.

Reaction of Ethoxyacetaldehyde Diethyl Acetal with Phenylhydrazine and Boron Trifluoride Etherate. Phenylhydrazine 10.8 g. (0.1 mole) in 100 ml. glacial acetic acid containing 16.2 g. (0.1 mole) ethoxyacetaldehyde diethyl acetal was treated with 15.1 g. (0.10 mole) of boron trifluoride etherate. There followed a highly exothermic reaction resulting in the formation of much tar. The products were poured into 1 l. of water and neutralized with sodium bicarbonate. The precipitated tarry material was insoluble in ether. An acetone extract upon which a thin layer chromatogram was run using benzene as eluant, gave no evidence supporting the formation of 3-ethoxyindole.

An authentic sample of 3-ethoxyindole 1.0 g. ( $6.21 \times 10^{-4}$  mole) when treated with approximately 5 drops of boron trifluoride etherate, underwent immediate decomposition, depositing a dark amorphous material.

3-(2-Carbethoxyindolyl) p-Toluenesulphonate. A solution of 24 g. (0.117 mole) of 2-carbethoxyindoxyl (101) in 200 ml. of pyridine at -20° was added to a solution of 22.5 g. (0.118 mole) of p-toluenesulphonyl chloride in 200 ml. of pyridine at -20°. The



resulting mixture was allowed to stand overnight at room temperature, then poured into 2 l. of cold water. The precipitated yellowish organic material solidified on standing for a few hours. Filtration of the material and crystallization from ethyl alcohol produced 35 g. (83.4%) of 3-(2-carbethoxyindolyl) p-toluenesulphonate melting at 151-153°. An analytical sample was prepared by recrystallization from toluene yielding a colourless compound melting at 153°.

Calc. for  $C_{18}H_{17}O_5NS$ : C, 60.35; H, 4.73; N, 3.90; S, 8.92.

Found: C, 60.01; H, 4.76; N, 3.97; S, 9.19.

Infrared analysis shows characteristic indolic  $>N-H$  absorption at  $3290\text{ cm}^{-1}$  (Fig. 20, page 84). A nuclear magnetic resonance spectrum in pyridine (Fig. 21, page 89) indicated a triplet at  $8.78\tau^*$ , a quartet at  $5.72\tau^*$  both characteristic of the ethyl group, and a singlet at  $7.78\tau$  due to the methyl group attached to the benzene ring.

Reaction of 3-(2-Carbethoxyindolyl) p-Toluenesulphonate with Thioglycolic Acid. A mixture of sodium (1.34 g., 0.0582 mole) dissolved in 500 ml. of anhydrous ethyl alcohol was treated with 2.67 g. (0.0288 mole) of thioglycolic acid. There appeared a heavy colourless precipitate. To this mixture was added 10 g. (0.0278 mole) of 3-(2-carbethoxyindolyl) p-toluenesulphonate and the mixture was then refluxed overnight. The cooled reaction products were poured into 2 l. of cold water and acidified with acetic acid. Filtration of the precipitated material yielded 2 g. (35%) of 2-carbethoxyindoxyl melting at 110-112°. Admixture with authentic material gave a melting point of 110-113°. An

\*J=7 c.p.s.





infrared spectrum was identical with that of the authentic material.

Changing the solvent to diglyme or dimethylformamide, or replacing the thioglycolic acid by ethyl mercaptan in each of these solvents yielded the same result.

1,2-Dithiolo[4,3-b]indole-3(4H)-thione. 2-Carbethoxyindoxyl (10 g., 0.0278 mole) in 150 ml. of xylene (practical grade) was treated with 20 g. (0.09 mole) of phosphorus pentasulphide. The resulting mixture was refluxed 2½ hours and filtered while hot. The volume was reduced to about 50 ml. and chromatographed on neutral alumina (activity grade 1) using ether as eluant. Evaporation of the ether deposited deep orange crystals, which upon crystallization from toluene gave 1.2 g. (11.1%) of orange crystals melting at 208° (dec.).

Calc. for C<sub>9</sub>H<sub>5</sub>NS<sub>3</sub>: C, 48.40; H, 2.24; N, 6.28; S, 43.10.

Found: C, 48.53; H, 2.35; N, 6.42; S, 43.07.

Molecular weight by the Rast procedure, 231; by mass spectrometry, 223. Calc. molecular weight, 223. An infrared spectrum run in nujol (Fig. 22, page 92) showed indolic >NH absorption at 3310 cm<sup>-1</sup>. A nuclear magnetic resonance spectrum obtained from a dimethylsulphoxide solution of the compound showed >N-H absorption at -2.34 $\tau$ , and aromatic proton absorption between 1.8 and 3.0 $\tau$  (Fig. 23, page 93). The n.m.r. spectrum in pyridine (Fig. 24, page 94) showed a signal for >N-H at -2.29 $\tau$ . The compound did not react with Ehrlich's reagent. Active Raney nickel (40 g.) in 200 ml. of 95% ethyl alcohol containing 300 mg. (0.0013 mole) of 1,2-dithiolo[4,3-b]indole-3(4H)-thione was refluxed 24 hours. The reaction mixture was filtered hot, and the Raney nickel





extracted with hot ethyl alcohol (3 x 100 ml.). Combination of the ethanolic solutions and evaporation of solvent yielded approximately 10 mg. of a compound regarded as 2-methylindole (comparative I.R. Fig. 25, page 95).

Ethyl 3-(ethylthio)-2-indoledithiocarboxylate. A mixture of 1,2-dithiolo[4,3-b]indole-3(4H)-thione 3.0 g. (0.0135 mole) in 50 ml. of 95% ethyl alcohol and 10 ml. of water was treated with 0.5 g. (0.0133 mole) of sodium borohydride under an atmosphere of nitrogen. The mixture was then heated to reflux for 30 minutes. To the cooled solution was added 2 g. (0.05 mole) of sodium hydroxide followed by 4.4 g. (0.0282 mole) of ethyl iodide and the solution brought to reflux for an additional 30 minutes. During this process the originally dark red solution became light orange. The reaction mixture was filtered and upon addition of water to the filtrate followed by standing in the refrigerator at  $-10^{\circ}$  for 2 days deposited light orange needles melting at  $43-45^{\circ}$ . Yield, 3.17 g. (84%). An analytical sample, prepared by recrystallization from toluene, melted at  $44-45^{\circ}$ .

Calc. for  $C_{13}H_{15}NS_3$ : C, 55.50; H, 5.34; N, 4.98; S, 34.15.

Found: C, 55.24; H, 5.14; N, 5.21; S, 34.50.

An infrared spectrum obtained in nujol showed  $>N-H$  absorption at  $3340\text{ cm}^{-1}$  (Fig. 26, page 95). A nuclear magnetic resonance spectrum run in  $CDCl_3$  (Fig. 27, page 97) indicated two triplets at  $8.58\gamma^*$  and  $8.8\gamma^{**}$  and two quartets centred at  $6.6\gamma^{\dagger}$  and  $7.1\gamma^{\dagger}$ . These are strongly indicative of two ethyl groups. Aromatic proton absorption occurred at  $2-3\gamma$ . The integrated areas corresponded with the structure designated.

\*  $J=7.5\text{ c.p.s.}$       \* \*  $J=7.5\text{ c.p.s.}$

$\dagger J=7.5\text{ c.p.s.}$



Hydrolysis of Ethyl 3-(ethylthio)-2-indoledithiocarboxylate.

Two grams ( $7.13 \times 10^{-3}$  mole) of ethyl 3-(ethylthio)-2-indoledithiocarboxylate was refluxed in 50 ml. of a 1:1 ethanol-water solution containing 4.0 g. (0.0715 mole) of KOH for 2 hours during which time the odour of ethyl mercaptan was observed. Acidification of the cooled reaction mixture yielded 500 mg. (33%) of crude material melting at  $74-76^{\circ}$  and production of  $H_2S$ . The compound was base soluble and could be reprecipitated upon addition of acid. The substance was suspected to be either 3-ethylthioindole-2-carboxylic acid or 3-ethylthioindole-2-thiolocarboxylic acid. An infrared spectrum run in nujol (Fig. 28, page 99) indicated  $>N-H$  absorption at  $3310\text{ cm}^{-1}$ ,  $>C=O$  absorption at  $1695\text{ cm}^{-1}$ . An analytical sample was prepared by recrystallization from ethanol-water, and melted at  $75-77^{\circ}$ .

3-Ethylthioindole (Method 2). 3-Ethylthioindole-2-carboxylic acid (380 mg.,  $1.8 \times 10^{-3}$  mole) was heated at  $150^{\circ}/6\text{ mm.}$ . A gas was evolved and a liquid distilled under these conditions affording 85 mg. (26.6%) of pure 3-ethylthioindole identical in boiling point, infrared and nuclear magnetic resonance spectra with those of an authentic sample. (Fig. 19, page 83 and Fig. 31, page 147).

Carbethoxymethyl 3-carbethoxymethylthioindole-2-dithiocarboxylate. 1,2-Dithiolo[4,3-b]indole-3(4H)-thione, 2.0 g. (0.009 mole) in 100 ml. of 95% ethyl alcohol was treated with 1.0 g. (0.0263 mole) of sodium borohydride under an atmosphere of nitrogen. Upon completion of the borohydride reduction, the products were refluxed for 30 minutes. After the addition of 10 ml. of water, 2.5 g. (0.015 mole) of ethyl bromoacetate was added and the mixture once







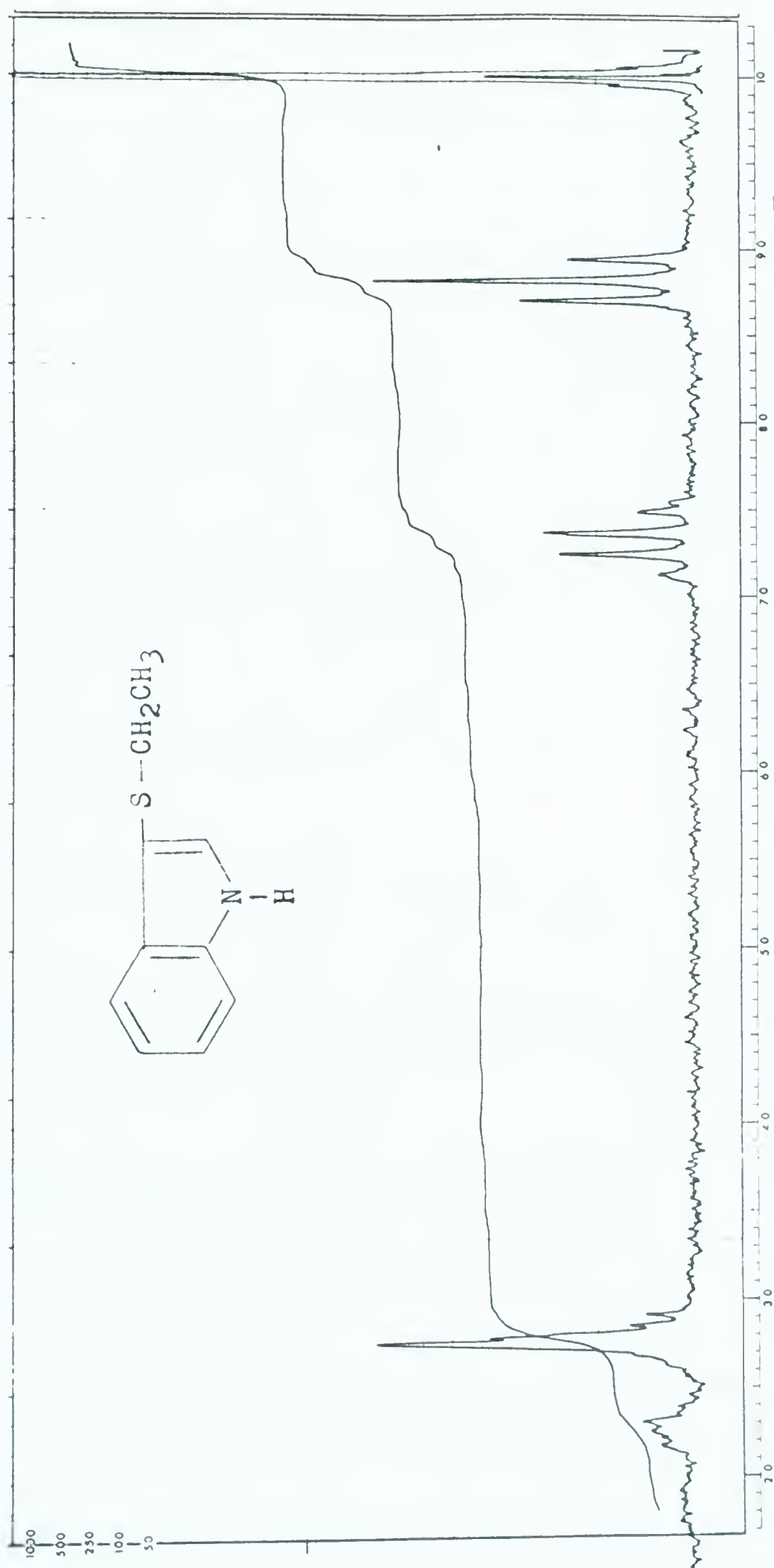


Fig. 31. N.M.R. Spectrum of 3-Ethylthioindole.

(Solvent, Deuteriochloroform. Reference - Tetramethylsilane.)



again refluxed for 30 minutes. When the reaction mixture was cooled and water added there was deposited 2.5 g. (68%) of carbethoxymethyl 3-carbethoxymethylthioindole-2-dithiocarboxylate melting at 109-110°. An analytical sample was prepared by recrystallization from toluene and melted at 108-110°. Infrared analysis in CHCl<sub>3</sub> (Fig. 29, page 102) indicated >N-H by absorption at 3390 cm<sup>-1</sup> and >C=O due to absorption at 1720 cm<sup>-1</sup>. A nuclear magnetic resonance spectrum (Fig. 29, page 102) showed two triplets centred at 8.71 $\gamma$ <sup>\*</sup> and 8.96 $\gamma$ <sup>\*</sup>, two singlets at 5.78 $\gamma$  and 6.46 $\gamma$ . Two quartets were found between 5.5 $\gamma$ <sup>\*</sup> and 6.3 $\gamma$ <sup>\*</sup> while aromatic protons were observed between 2 and 3 $\gamma$ . The two sets of triplets and quartets are indicative of two ethyl groups while the two singlets are assigned to the two slightly different methylene units.

Calc. for C<sub>17</sub>H<sub>19</sub>O<sub>4</sub>NS<sub>3</sub>: C, 51.45; H, 4.79; N, 3.53; S, 24.20.

Found: C, 51.61; H, 4.60; N, 3.74; S, 24.42.

#### 4. Experiments Involving Nuclear Magnetic Resonance Studies.

##### Deuteration

General Procedure. The following general procedure was employed in all deuteration. About 120 mg. of the indole compound was dissolved in 8 ml. of reagent acetone and then 2 ml. of D<sub>2</sub>O (99.7%) was added. The resulting solution was freed of solvent in a rotary evaporator under vacuum. This treatment was repeated two or three times. Final drying was carried out in a desiccator over P<sub>2</sub>O<sub>5</sub>. Care was taken to protect the solutions from direct light.

\* J = 7.5 c.p.s.



The extent of deuteration was determined by infrared spectrometry and by n.m.r.. Disappearance of the  $>\text{N}-\text{H}$  peak between 3100 and 3500  $\text{cm}^{-1}$  in the infrared and the appearance of a new peak due to  $>\text{N}-\text{D}$  at a frequency of about 0.75 of that of the  $>\text{N}-\text{H}$  stretching gave a measure of the amount of deuteration. N-Deuteration was more rapid for the indoles containing electro-negative substituents in the 2 or 3 positions. For indole and 2-substituted indoles, considerable deuteration occurred at the 3 position, as detected by the lower integrated area for the 3 proton signal in the N-deuterated compounds.

Dedeuteration, both at the nitrogen atom and at the 3 carbon, occurred readily when the compounds were dissolved in 95% ethanol and the solvent evaporated.

N-Deutero-3-bromoindole. Since 3-bromoindole decomposes spontaneously when its solution is completely freed of solvent, the following procedure was employed. A quantity of 3-bromoindole (5.0 g., 0.025 mole) was treated with 2 ml. of  $\text{D}_2\text{O}$  (99.7%). The solution was concentrated at room temperature under vacuum by rotary evaporator almost to dryness, then acetone and  $\text{D}_2\text{O}$  added again and the process repeated. The concentrated solution now was poured into 100 ml. of n-heptane to which 5 g. of anhydrous magnesium sulphate was then added. After addition of decolorizing charcoal, the mixture was stirred vigorously and heated to the boiling point. As long as the 3-bromoindole was in solution it could be heated above its normal decomposition temperature ( $67^\circ$ ) with no ill effect. The boiling solution was quickly filtered into a cooled receiver. Cooling is essential since 3-bromoindole





deposited at a temperature close to or above its decomposition point will spontaneously decompose. The N-deutero-3-bromoindole crystallized as plates in a yield of 80%, melting at 65-66° (dec.).

N,3-Dideuteroindole. A solution of indole (11.7 g., 0.1 mole) in ether (50 ml.) was added slowly to an ether solution of 0.2 mole of ethylmagnesium iodide (from 4.8g., 0.2 mole, of magnesium and 31.2 g., 0.2 mole, of ethyl iodide in 250 ml. of ether). When reaction was complete the solution, protected from moisture, was cooled to 0° and then stirred rapidly while 10 ml. of D<sub>2</sub>O (99.7%) in 50 ml. of anhydrous tetrahydrofuran was added dropwise. When addition was complete, the solution was refluxed overnight. The cooled mixture was then filtered rapidly to minimize admission of water since this causes rapid dedeuteration. The solvent was then removed completely by rotary evaporator under vacuum. Sufficient hot n-heptane was then added to dissolve the indole which had precipitated. The resulting clear solution was dried (MgSO<sub>4</sub>) and filtered. When the solution was cooled and allowed to stand overnight the dideuteroindole separated. The solid was quickly isolated by filtration, and dried under nitrogen in a desiccator. Yield, 6 g. (51%). The n.m.r. analysis indicated that the 3 position was deuterated approximately to the extent of 50%. Infra-red analysis showed that the nitrogen atom was deuterated approximately to the extent of 50%.

2-Benzoylindole. (Fig. 33, page 151). Thionyl chloride (22 ml.) was slowly added to 12.3 g. (0.075 mole) of solid, powdered indole-2-carboxylic acid. When the initial vigorous reaction had subsided, the mixture was heated for 20 minutes on a steam bath.



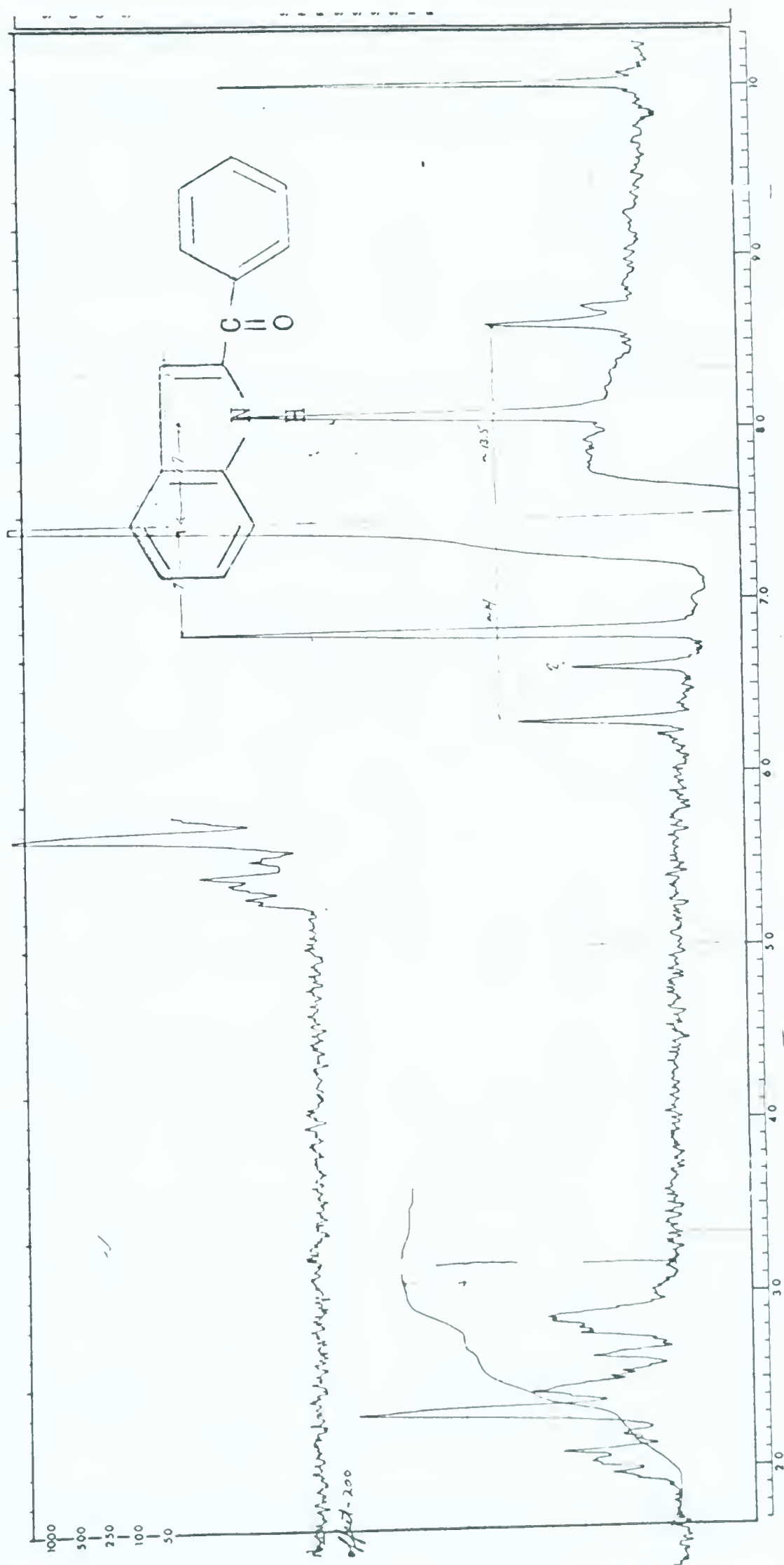


Fig. 33. N.M.R. Spectrum of 2-Benzoylindole.

(Solvent, Dimethylsulphoxide. Reference - Tetramethylsilane.)





Excess thionyl chloride was removed under vacuum. The solid product was taken up in 50 ml. of dioxane and the solution then slowly added to 50 g. (0.19 mole) of diphenyl cadmium (142) dissolved in 300 ml. of benzene. The reaction mixture was then heated under reflux for 12 hours. The cooled solution was poured slowly, with stirring, onto 2 kg. of ice, while sufficient acetic acid was added to maintain approximately a pH of 7 (hydrion paper). The benzene layer was separated and treated with ether to precipitate the 2-benzoylindole. The crude precipitate was extracted with pentane for 24 hours in a Soxhlet apparatus. The pentane extract was freed from solvent and the residue crystallized from a mixture of ethanol and water. There was obtained 5.4 g. (32%) of colorless needles melting at  $146-148^{\circ}$ . The infrared spectrum in  $\text{CHCl}_3$  showed  $\text{N}-\text{H}$  stretching at  $3452\text{ cm}^{-1}$ , bonded  $\text{N}-\text{H}$  at  $3325\text{ cm}^{-1}$  and carbonyl stretching at  $1625\text{ cm}^{-1}$ .

Calc. for  $\text{C}_{15}\text{H}_{11}\text{NO}$ : C, 81.45; H, 4.88; N, 6.33; O, 7.24.

Found: C, 81.19; H, 5.37; N, 6.36; O, 7.21.

3-Acetyl-2-methylindole. The procedure for the preparation of this compound as described in the literature (140) failed to give satisfactory results. Accordingly the following method was devised. A solution of 4 g. (0.033 mole) of 2-methylindole in ether was added slowly to ethyl magnesium iodide (from 1.6 g., 0.067 mole, of magnesium metal and 9.6 g., 0.065 mole, of ethyl iodide) in 100 ml. of ether. When addition was complete, the resulting solution was cooled to  $0^{\circ}$  and then 2.6 g. (0.033 mole) of acetyl chloride in 10 ml. of ether was added dropwise so that the temperature of the mixture remained below  $5^{\circ}$ . Then the mix-



ture, continually stirred, was allowed to come to room temperature overnight. The contents of the reaction vessel was poured onto ice (200 g.) along with sufficient acetic acid to react with the magnesium hydroxide produced. The precipitated 3-acetyl-2-methylindole was removed by filtration and crystallized from aqueous ethanol to yield 3.2 g. (56.5%) of pure product melting sharply at  $204^{\circ}$  (lit.,  $195-196^{\circ}$  (140)). An n.m.r. spectrum in dimethylformamide indicated acetyl methyl at  $7.44\tau$ , 2-methyl buried in the signal due to solvent at about  $7.08\tau$ , and a broad signal at  $-2.24\tau$  due to  $\text{>N-H}$ . In pyridine the respective  $\tau$  values for acetyl methyl and 2-methyl were clearly separated and discernible at 7.34, 7.22. Infrared spectra in halo oil showed  $\text{>N-H}$  stretching at  $3082\text{ cm}^{-1}$ , and carbonyl absorption at  $1605\text{ cm}^{-1}$ .

Ethyl Indole-2-carboxylate. A solution of indole-2-carboxylic acid (5.0 g., 0.31 mole) in 50 ml. of anhydrous ethyl alcohol, saturated with anhydrous hydrogen chloride, was allowed to stand overnight. The mixture was poured into water and made slightly basic with dilute caustic soda. The cold, basified solution was twice extracted with 100 ml. portions of ether. Removal of the ether and crystallization of the residue from aqueous ethanol gave long needles melting at  $125^{\circ}$ . Lit.,  $125-126^{\circ}$  (141). Yield 74.5%. Infrared spectra in nujol showed  $\text{>N-H}$  stretching at  $3310\text{ cm}^{-1}$  and carbonyl absorption at  $1685\text{ cm}^{-1}$ .



## APPENDIX

### Determination of Molecular Formulae.

The method described by Silverstein and Bassler (125) is used to determine the molecular formula of the following:

(a) The product obtained by a Fischer cyclization of the phenylhydrazone of ethylthioacetaldehyde was analyzed on a mass spectrometer. There was found a large parent+ 2 peak (5.37%) which is strongly indicative of a single atom of sulphur, due to the  $^{34}_{16}\text{S}$  isotope of sulphur (Table IV).

TABLE IV

#### Principal Stable Isotopes and Relative Abundances\*

<u>Isotopes</u>	<u>Per Cent of Isotope of Lowest Mass</u>
$^{13}_6\text{C}$	1.1
$^2_1\text{H}$	0.015
$^{18}_8\text{O}$	0.2
$^{15}_7\text{N}$	0.37
$^{33}_{16}\text{S}$	0.78
$^{34}_{16}\text{S}$	4.4
$^{37}_{17}\text{Cl}$	32.5
$^{81}_{35}\text{Br}$	98.0

\*These data are obtained from figures shown by Beynon (126).

Subtracting an atom of sulphur from the observed molecular weight of 177, one obtains a value of 145. Under the value of





145 Beynon (126) lists 33 combinations of C,H,N and O. These values are calculated on the basis of isotope abundance ratios.

Since the molecular weight is uneven, and the presence of nitrogen is indicated ( $>$ N-H absorption in the infrared) it was concluded from the nitrogen rule (126) that an uneven number of nitrogen atoms exist in this particular molecule. This allows elimination of eighteen of the formulae from Beynon's table.

The parent+1 peak of 12.4, corrected to 11.62 (due to the isotope  $^{33}_{16}\text{S}$ , Table IV), and the parent+2 peak fall in the region  $P + 1 \simeq 12$  and  $P + 2 \simeq 5$ . In this region Beynon lists the following empirical formulae (Table V).

TABLE V

<u>Empirical Formulae</u>		<u>P + 1</u>	<u>P + 2</u>
(1)	$\text{C}_9\text{H}_7\text{NO}$	10.258	6.733
(2)	$\text{C}_{10}\text{H}_9\text{O}$	10.989	7.459
(3)	$\text{C}_{10}\text{H}_{11}\text{N}$	11.363	5.865

The best fit is obviously  $\text{C}_{10}\text{H}_{11}\text{N}$ , which with the addition of an atom of sulphur, provides us with  $\text{C}_{10}\text{H}_{11}\text{NS}$ , or that required by theory for 3-ethylthioindole.

(b) A compound regarded as 1,2-dithiolo[4,3-b]indolo-3(4H)-thione was analyzed in a similar manner with results in general agreement with those required by this compound.



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